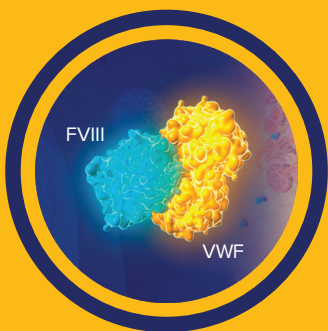


POWERED BY PLASMA

THINK KOATE® [Antihemophilic Factor (Human)]



Learn about managing
hemophilia A with
KOATE, a plasma-
derived FVIII/VWF*
complex product.

*FVIII: factor VIII; VWF:
von Willebrand factor.



Not an actual
KOATE patient

APPROVED USE

KOATE (Antihemophilic Factor (Human)) is a medicine used 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). KOATE is not approved for the treatment of von Willebrand disease.

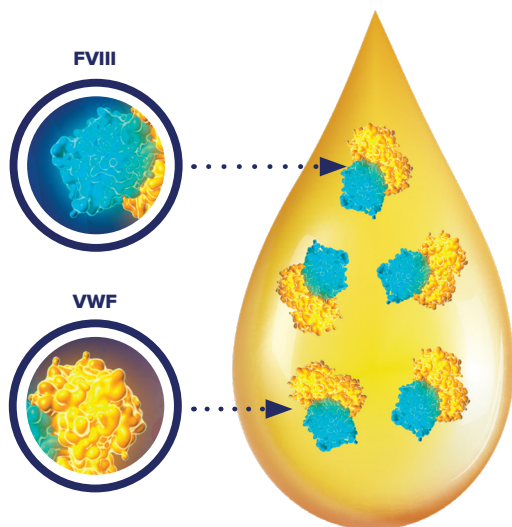
IMPORTANT SAFETY INFORMATION

- Do not use KOATE if you have had an allergic reaction to KOATE or any of its components.

Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

THINK KOATE® [Antihemophilic Factor (Human)]

... KOATE is a protein-rich plasma-derived FVIII/VWF replacement therapy that replaces missing or nonfunctional FVIII to help **control and prevent bleeds** in people with hemophilia A.¹



POWERED BY PLASMA^{1,2}

KOATE is a *plasma-derived* FVIII/VWF complex product, meaning that it is created from blood plasma donated by healthy people.

- **No two** plasma-derived therapies are exactly alike
- **No two** people will respond exactly the same way to a single therapy

IMPORTANT SAFETY INFORMATION

- Do not use KOATE if you have had an allergic reaction to KOATE or any of its components.
- Tell your healthcare provider about all of your medical conditions, including any medicines you take, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.

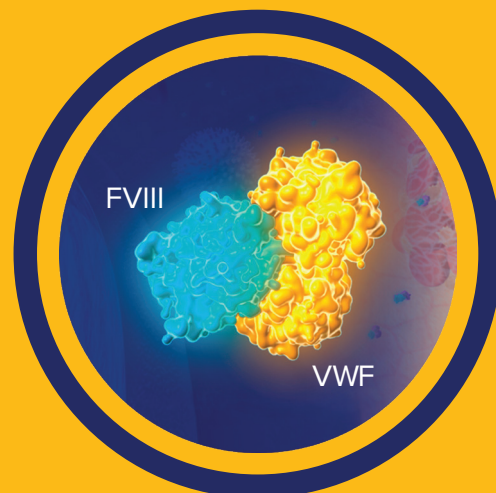
THE ROLE OF VWF^{1,3}

In the body, FVIII is **naturally bound** to another clotting factor protein called von Willebrand factor (VWF).*

VWF is an important protein that helps blood clot by **binding to and stabilizing FVIII** and **transporting FVIII** to the site of a bleed.

KOATE is purified from human plasma and contains **naturally occurring VWF**, which is co-purified during the manufacturing process.

*KOATE is not approved for the treatment of von Willebrand disease.



Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

Not an actual KOATE patient

COMMITTED TO SAFETY¹⁻⁴

Each step in the manufacturing process is designed to **increase the safety** of KOATE.

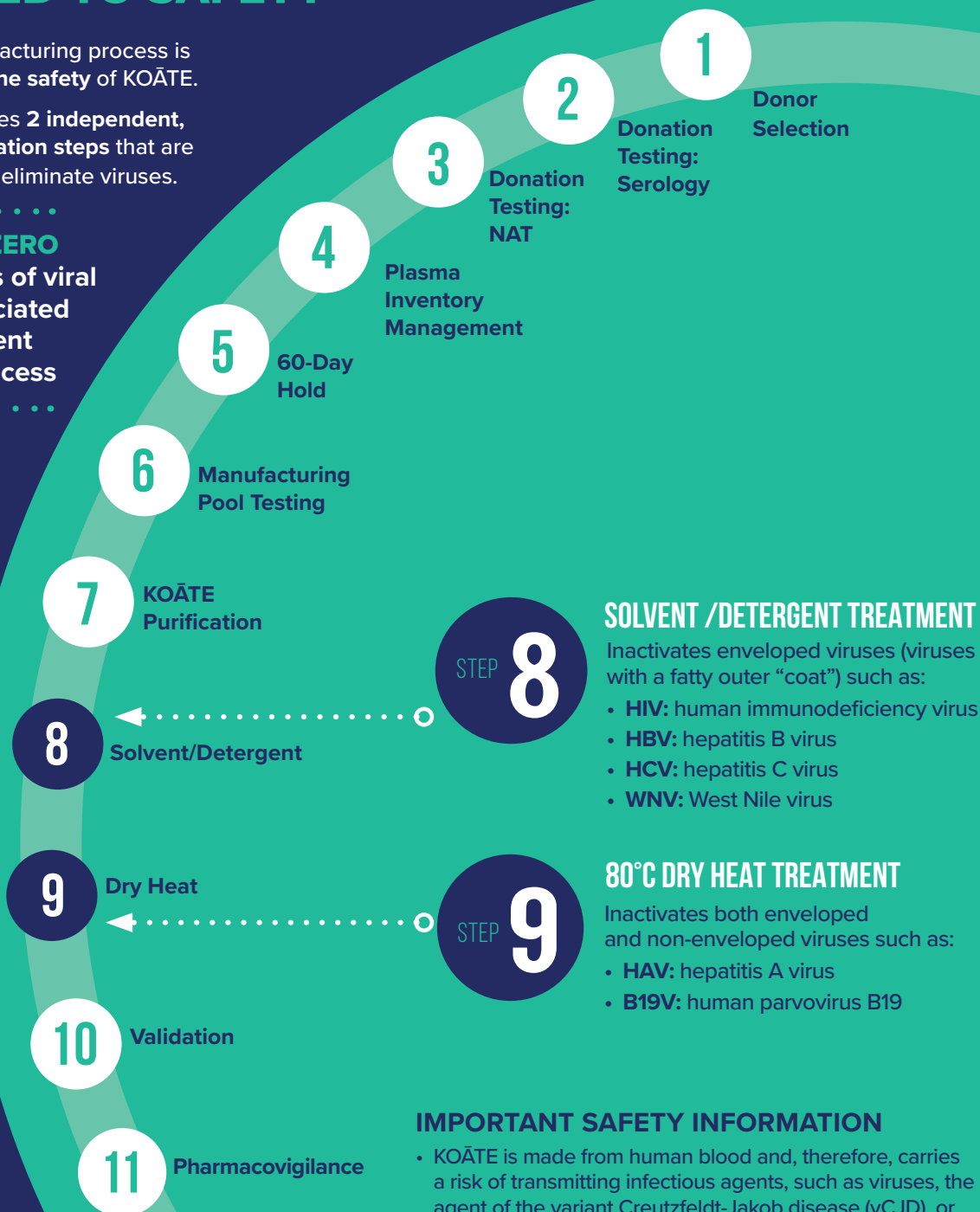
Additionally, KOATE uses **2 independent, dedicated viral inactivation steps** that are proven to inactivate or eliminate viruses.

.....

There have been **ZERO** documented cases of viral transmission associated with KOATE's current manufacturing process

.....

THINK
KOATE[®]
[Antihemophilic
Factor (Human)]
POWERED BY PLASMA



IMPORTANT SAFETY INFORMATION

- KOATE is made from human blood and, therefore, carries a risk of transmitting infectious agents, such as viruses, the agent of the variant Creutzfeldt-Jakob disease (vCJD), or unknown infectious agents. You should consult with your healthcare provider if you have any questions or concerns.

Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

IMPORTANT PRODUCT FEATURES^{1,5}

THINK
KOĀTE[®]
[Antihemophilic
Factor (Human)]

16.1

16.1 hour mean biologic half-life

0.7%

0.7% - a low risk of side effects per infusion (7 out of 1053 infusions were associated with a side effect in the clinical study of 19 patients)*

*10 adverse reactions related to 7 infusions were reported in 4 of 19 patients.

82%

82% of bleeding episodes (251 out of 306) were effectively managed with a single KOĀTE infusion in the clinical study of 19 patients

0

No inhibitors developed during KOĀTE's clinical study*†

*In 34 previously treated patients over the course of 6 months of treatment. Median number of exposure days was more than 50 days (range of 23-94).

†Inhibitors may form with the use of KOĀTE. Your healthcare provider will monitor you for the development of inhibitors.

Not an actual
KOĀTE patient

IMPORTANT SAFETY INFORMATION

- Antibodies neutralizing Factor VIII (also known as inhibitors), which can make the product less effective or ineffective, may form with use of KOĀTE. Your healthcare provider will monitor you for the development of inhibitors.

- In a clinical study, the most common side effects associated with the infusion of KOĀTE were nervousness, headache, abdominal pain (stomach ache), nausea, tingling sensation and blurred vision.

Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

NEEDLE-FREE RECONSTITUTION¹

PACKAGED WITH A
MIX2VIAL[®]



KOATE is **administered intravenously** (into a vein) after reconstitution. KOATE is supplied in powdered form and must be mixed with sterile diluent prior to administration.

Every vial of KOATE comes with a Mix2Vial[®] transfer device, allowing for **needle-free reconstitution**.

KOATE is supplied in single-use vials in the following sizes:

● 250 IU ● 500 IU ● 1,000 IU

The exact number of IUs per vial is stated on each carton and vial label. Use this number to achieve your prescribed dose.

ASK YOUR HEALTHCARE
PROVIDER ABOUT THE
MIX2VIAL[®]
Practice Kit



KOATE[®]
[Antihemophilic Factor (Human)]

ADMINISTRATION FAQS¹

- **Can KOATE be self-administered?**
- Yes! You or a caregiver can be trained to administer KOATE in the comfort of your own home. See the KOATE Full Prescribing Information for detailed administration instructions.
- **How often is KOATE administered?**
- Dose and frequency of infusions vary from person to person. Your doctor will determine the appropriate amount of KOATE for you or your child based on your specific clinical condition.
- **How do I store KOATE?**
- KOATE can be stored at room temperature for up to 6 months or can be stored refrigerated.* Store KOATE in its original packaging to protect it from light. Do not freeze KOATE and do not use after the expiration date.
- *Room temperature storage is up to 25°C (77°F). Refrigerated storage is 2°C to 8°C (36°F to 46°F).
- **How soon after reconstitution should KOATE be administered?**
- Since there are no preservatives in the vial, KOATE should be used immediately or within 3 hours of reconstitution.

IMPORTANT SAFETY INFORMATION

- There is a risk of increased breakdown of red blood cells (or hemolytic anemia) in patients with blood groups A, B or AB when large or frequent doses of KOATE are given. Your healthcare provider will monitor your levels of red blood cells and look out for signs of red blood cell breakdown.

Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

KEDRION CONNECT PATIENT ASSISTANCE PROGRAM

KEDRION CONNECT provides financial support for eligible patients in 2 ways.

SITUATION 1

You have commercial prescription drug coverage, but need help with co-pay costs for KOÅTE.

PROGRAM CONNECTION

The Co-Pay Assistance Program helps eligible patients with their co-pay costs.

The Co-Pay Card covers up to a total of \$16,000 per calendar year.

SITUATION 2

You have private insurance coverage, but cannot pay your insurance premiums.

PROGRAM CONNECTION

The Insurance Premium Support Program helps with private insurance premiums and assistance for those who qualify.

KOÅTE TRY-IT PROGRAM

- The KOÅTE TRY-IT Program* allows eligible patients to try KOÅTE for up to 2 weeks at no cost
- To be eligible for the program, you must not currently use KOÅTE and must not have a currently diagnosed inhibitor
- The 2-week free trial may not exceed 50,000 IUs of KOÅTE

*Terms, conditions, and eligibility criteria apply. Talk to your doctor for details.

Talk to your doctor to find out if you qualify for **KEDRION CONNECT** or the **KOÅTE TRY-IT PROGRAM**.



Not an actual
KOÅTE patient

Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

**RECENTLY
DIAGNOSED
WITH
HEMOPHILIA A?**

**LOOKING
FOR AN
ALTERNATIVE
FVIII
THERAPY?**

**LIVING
WITH A FVIII
INHIBITOR?**

**UNDERGOING
SURGERY?**

**NEW TO FVIII
THERAPY?**

**THINK
KOĀTE[®]**
[Antihemophilic
Factor (Human)]

NOTES

IMPORTANT SAFETY INFORMATION

- Tell your healthcare provider about all of your medical conditions, including any medicines you take, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.

Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

Not an actual
KOĀTE patient



IMPORTANT SAFETY INFORMATION

- Do not use KOÅTE if you have had an allergic reaction to KOÅTE or any of its components.
- Tell your healthcare provider about all of your medical conditions, including any medicines you take, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
- Allergic reactions, including serious, life-threatening allergic reactions, are possible from the administration of antihemophilic factor preparations such as KOÅTE. Immediately report any of the following signs or symptoms of an allergic reaction to your healthcare provider: swelling of the throat, tightness of the chest, low blood pressure, rash, nausea, vomiting, a tingling or pricking sensation, restlessness, wheezing or shortness of breath.
- Antibodies neutralizing Factor VIII (also known as inhibitors), which can make the product less effective or ineffective, may form with use of KOÅTE. Your healthcare provider will monitor you for the development of inhibitors.
- There is a risk of increased breakdown of red blood cells (or hemolytic anemia) in patients with blood groups A, B or AB when large or frequent doses of KOÅTE are given. Your healthcare provider will monitor your levels of red blood cells and look out for signs of red blood cell breakdown.
- KOÅTE is made from human blood and, therefore, carries a risk of transmitting infectious agents, such as viruses, the agent of the variant Creutzfeldt-Jakob disease (vCJD), or unknown infectious agents. You should consult with your healthcare provider if you have any questions or concerns.
- In a clinical study, the most common side effects associated with the infusion of KOÅTE were nervousness, headache, abdominal pain (stomach ache), nausea, tingling sensation and blurred vision.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/MedWatch, or call 1-800-FDA-1088.

Please see the accompanying Full Prescribing Information.



References: **1.** KOÅTE [prescribing information]. Fort Lee, NJ. Kedrion Biopharma Inc. 2018. **2.** Hemophilia Treatment. Centers for Disease Control and Prevention website. <https://www.cdc.gov/ncbddd/hemophilia/treatment.html>. Accessed June 3, 2019. **3.** De Meyer SF, Deckmyn H, Vanhoorelbeke K. von Willebrand factor to the rescue. *Blood*. 2009;113(21):5049-57. **4.** Data on file. **5.** Powell JS, Bush M, Harrison J, et al. Safety and efficacy of solvent/detergent-treated antihaemophilic factor with an added 80°C terminal dry heat treatment in patients with haemophilia A. *Haemophilia*. 2000;6:140-149.

ARE YOU MEETING YOUR TREATMENT GOALS?^{1,4}



• **Ask your doctor about controlling and preventing bleeds with KOATE, a protein-rich plasma-derived FVIII/VWF complex product for people with hemophilia A.**

- Contains naturally-occurring VWF*
- 16.1-hour mean biologic half-life
- 2 independent, dedicated viral inactivation steps in manufacturing
- 0 cases of viral transmission associated with current manufacturing process
- 82% of bleeds effectively managed with a single dose
- 0.7% - a low risk of side effects per infusion
- Needle-free reconstitution

*KOATE is not approved for the treatment of von Willebrand disease.

IMPORTANT SAFETY INFORMATION

- Allergic reactions, including serious, life-threatening allergic reactions, are possible from the administration of antihemophilic factor preparations such as KOATE. Immediately report any of the following signs or symptoms of an allergic reaction to your healthcare provider: swelling of the throat, tightness of the chest, low blood pressure, rash, nausea, vomiting, a tingling or pricking sensation, restlessness, wheezing or shortness of breath.

Please see the complete Important Safety Information on page 14 and the accompanying Full Prescribing Information.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KOATE® safely and effectively. See full prescribing information for KOATE.

KOATE®, Antihemophilic Factor (Human)

Lyophilized Powder for Solution for Intravenous Injection

Initial U.S. Approval: 1974

RECENT MAJOR CHANGES

Dosage and Administration (2.1, 2.2)	12/2015
Contraindications (4)	12/2015
Warnings and Precautions, Neutralizing Antibodies (5.2)	12/2015

INDICATIONS AND USAGE

KOATE 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). (1)

Limitation of Use

KOATE is not indicated for the treatment of von Willebrand disease.

DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

- Each vial of KOATE contains the labeled amount of Factor VIII in international units (IU). (2)
- Required Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5
- Frequency of KOATE administration is determined by the type of bleeding episode and the recommendation of the treating physician.

DOSAGE FORMS AND STRENGTHS

KOATE is available as a lyophilized powder for reconstitution in single-use vials of 250, 500, and 1,000 international units of Factor VIII activity. (3)

CONTRAINDICATIONS

Do not use in patients who have known hypersensitivity reactions, including anaphylaxis, to KOATE or its components. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, discontinue KOATE and administer appropriate treatment. (5.1)
- Development of neutralizing antibodies (inhibitors) may occur. 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. (5.2)
- Monitor for intravascular hemolysis and decreasing hematocrit values in patients with A, B or AB blood groups who are receiving large or frequent doses. (5.3)
- KOATE is made from human blood and therefore carries a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.4)

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)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>.

USE IN SPECIFIC POPULATIONS

Pediatric: clearance of Factor VIII (based on per kilogram body weight) is higher in children. Higher or more frequent dosing may be needed. (8.4)

See 17 for PATIENT COUNSELING INFORMATION. Revised: 6/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dose
- 2.2 Preparation and Reconstitution
- 2.3 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity Reactions
- 5.2 Neutralizing Antibodies
- 5.3 Intravascular Hemolysis

5.4 Transmissible Infectious Agents

5.5 Monitoring: Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

14 CLINICAL STUDIES

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16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KOÄTE® 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

KOÄTE 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.
- Each vial of KOÄTE is labeled with the actual Factor VIII potency 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.
- The required dose can be determined using the following formula:

$$\text{Dose (IU)} = \text{Body Weight (kg)} \times \text{Desired Factor VIII Rise (\% normal or IU/dL)} \times 0.5$$

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

$$\text{Estimated Increment of Factor VIII (\% normal or IU/dL)} = [\text{Total Dose (IU)/Body Weight (kg)}] \times 2$$

- 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

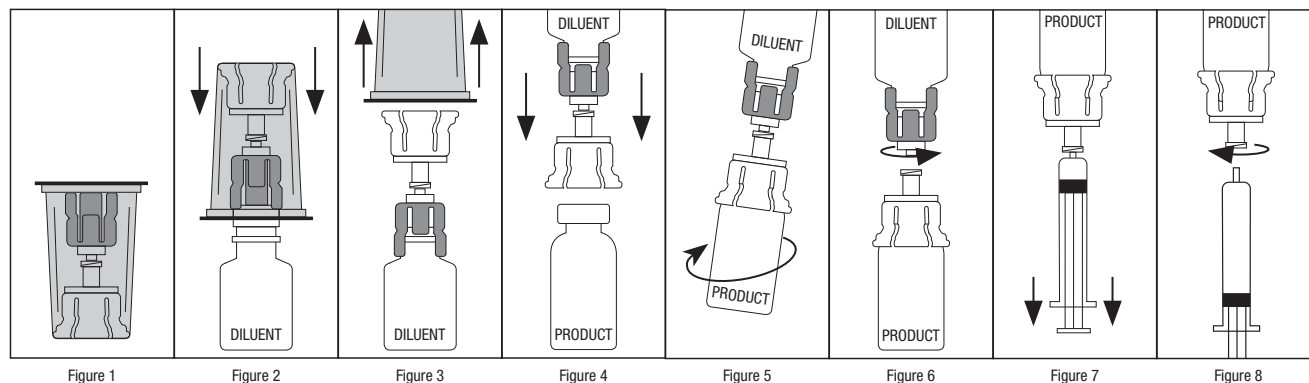
A guide for dosing KOÄTE for the control and prevention of bleeding episodes (1,2) is provided in Table 1. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

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.

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 and the diluent (Sterile Water for Injection) to room temperature before use.
3. Remove the shrink band from the KOATE vial. Do not use KOATE if the shrink band is absent or shows signs of tampering, and notify Grifols Therapeutics LLC immediately.
4. Remove the plastic cap from the KOATE vial 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. Open the sterile Mix2Vial® package by peeling away the lid (Figure 1). Do not remove the device from the package.
7. Place the diluent vial upright on an even surface. Holding the diluent vial securely, push the blue end of the Mix2Vial straight down until the spike penetrates the stopper (Figure 2).
8. Remove the clear outer packaging from the Mix2Vial and discard it (Figure 3).
9. Place the KOATE vial upright on a flat surface, and invert the diluent vial with the Mix2Vial still attached.
10. While holding the KOATE vial securely on a flat surface, push the clear end of the Mix2Vial straight down until the spike penetrates the stopper (Figure 4). The diluent will automatically transfer into the KOATE vial by the vacuum contained within it.
Note: If the Mix2Vial is connected at an angle, the vacuum may be released from the product vial and the diluent will not transfer into the product 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 vial, directing the stream of fluid against the wall of the vial.
11. With the diluent and KOATE vials still attached to the Mix2Vial, agitate vigorously for 10 to 15 seconds, then gently swirl (Figure 5) until the powder is completely dissolved. Avoid excessive foaming. The reconstituted solution should be clear to opalescent. Do not use if particulate matter or discoloration is observed.
12. Remove the diluent vial and the blue end of the Mix2Vial (Figure 6) by holding each side of the vial adapter and twisting counterclockwise.
13. Draw air into an empty, sterile syringe. Connect the syringe to the clear end of the Mix2Vial by pressing and twisting clockwise, and push the air into the KOATE vial.
14. Immediately invert the system upside down and then draw the reconstituted KOATE into the syringe by pulling the plunger back slowly (Figure 7).
15. Detach the filled syringe from the Mix2Vial by turning counter-clockwise (Figure 8). Use KOATE within 3 hours after reconstitution. Do not refrigerate after reconstitution.



2.3 Administration

For intravenous administration only

- If the dose requires more than one vial of KOATE:
 - Reconstitute each vial using a new Mix2Vial.
 - 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® (Antihemophilic Factor [Human]) 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 vial.

4 CONTRAINDICATIONS

KOATE is contraindicated in patients who have had hypersensitivity reactions, including anaphylaxis, to KOATE 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 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 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 and consider administering serologically compatible Type O red blood cells and providing alternative therapy.

5.4 Transmissible Infectious Agents

Because KOATE 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 to Grifols Therapeutics LLC at 1-800-520-2807.

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. 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.

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 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 KOÄTE 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 |

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with KOÄTE use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using KOÄTE. It is not known whether KOÄTE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. KOÄTE 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 KOÄTE 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 KOÄTE and any potential adverse effects on the breast-fed infant from KOÄTE 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 KOÄTE 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 KOÄTE 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

KOÄTE, 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 KOÄTE 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.

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

The KOÄTE 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 nonenveloped viruses (such as HAV and B19V). The polyethylene glycol (PEG) precipitation/depth filtration step has the capacity to remove both enveloped and nonenveloped viruses. The accumulated virus reduction factors for KOÄTE manufacturing process are presented in Table 2.

Table 2: Virus Clearance Capacity (Log₁₀) 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 KOÄTE 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 log₁₀ 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

KOÄTE 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 KOÄTE normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of KOÄTE 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 KOÄTE. Bioequivalence of the dry heat-treated KOÄTE to the unheated KOÄTE was demonstrated by comparison of C_{max} and the area under the curve, AUC₀₋₄₈ (Table 3). The incremental *in vivo* recovery ten minutes after infusion of dry heat-treated KOÄTE was 1.90% unit/kg (unheated KOÄTE was 1.82% units/kg). Mean biologic half-life was 16.1 hours.

In Stage II of the study, participants received KOÄTE 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 AUC₀₋₄₈ 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 KOÄTE (Stage I of Crossover Trial)

Parameter	KOÄTE Dry Heat-treated (mean ± SD)	KOÄTE 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 KOÄTE 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 KOÄTE with unheated KOÄTE. Nineteen subjects were randomized and received a single dose of 50 IU/kg of either heated KOÄTE or unheated KOÄTE for PK assessment. Stage II was a 6 month open-label safety study conducted at two hemophilia centers. Nineteen subjects received KOÄTE, 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

KOÄTE 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 and a Mix2Vial® transfer device. The actual amount of KOÄTE in IU is stated on each carton and vial label.

Components used in the packaging of KOÄTE are not made with natural rubber latex.

Strength	Carton (Kit) NDC Number
250 IU	76125-256-20 or 76125-257-25
500 IU	76125-668-30 or 76125-663-50
1,000 IU	76125-676-50 or 76125-678-10

Storage and Handling

- Store KOÄTE in its original package to protect it from light.
- Store the KOÄTE package at 2 to 8°C (36 to 46°F). Do not freeze.
- KOÄTE may also be stored at room temperature (up to 25°C or 77°F) for up to 6 months.
- Do not use after the expiration date.
- Use reconstituted KOÄTE immediately or within 3 hours of reconstitution.

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 KOÄTE. Advise the patients to contact their healthcare provider for further treatment and/or assessment if they experience a lack of clinical response to KOÄTE because this may be a manifestation of an inhibitor. *[see Warnings and Precautions (5.2)]*
- Inform patients that KOÄTE is made from human plasma and may carry a risk of transmitting infectious agents. While the risk that KOÄTE can transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating or removing certain viruses during manufacturing, patients should report any symptoms that concern them. *[see Warnings and Precautions (5.4)]*

Manufactured for:

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Manufactured by:

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