KOĀTE®
[Antihemophilic Factor (Human)]

SAFETY + COMMITMENT

WORKING TOGETHER,
Kedrion Biopharma and its partners are committed to the **SAFETY OF KOĀTE**

APPROVED USE

KOĀTE (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). KOĀTE is not approved for the treatment of von Willebrand disease.

Please see Important Safety Information throughout and the accompanying Full Prescribing Information.

KOĀTE®
[Antihemophilic Factor (Human)]

WHAT IS FVIII REPLACEMENT THERAPY?

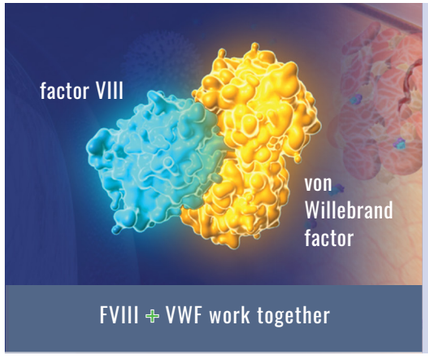
Hemophilia A and FVIII

Factor eight (FVIII) is a "clotting factor"—a protein in the blood that is needed in order for your blood to clot properly.[1]

Hemophilia A is an inherited bleeding disorder in which there is not enough working FVIII in the body to allow blood to clot. People with hemophilia A bleed longer and more frequently than other people.[1]

The most common treatment for hemophilia A is FVIII replacement therapy, where FVIII is infused (administered through a vein) to replace the missing or nonfunctional FVIII in the blood.[2]

KOĀTE is a plasma-derived replacement FVIII product, meaning that it is purified from blood plasma donated by healthy people.[2]



- In the body, FVIII is naturally bound to a protein called von Willebrand factor (VWF)[3]*
- VWF is important for FVIII stability and for transporting FVIII to the site of injury[3]
- **KOĀTE contains naturally occurring VWF, which is co-purified during the manufacturing process[4]**

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

IMPORTANT SAFETY INFORMATION

- Do not use KOĀTE if you have had an allergic reaction to KOĀTE 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.

Committed to safety at every step

The starting material for KOĀTE is human plasma, the straw-colored, liquid portion of the blood in which blood cells are suspended. Because clotting factors like FVIII make up only a small portion of the proteins found in plasma, KOĀTE is made from plasma collected from many US donors.

In this booklet, you will learn how KOĀTE is manufactured, beginning with strict donor screening and testing and ending with 2 dedicated viral inactivation steps.

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

There have been ZERO documented cases of viral transmission associated with KOĀTE's current manufacturing process[5]

Please note KOĀTE is made from human blood and, therefore, still carries a risk of transmitting infectious agents.

Please see Important Safety Information throughout and the accompanying Full Prescribing Information.

MANUFACTURING BEGINS WITH SELECTION OF QUALIFIED US DONORS AND RIGOROUS DONATION TESTING

1. DONOR SELECTION: ONLY QUALIFIED DONORS* PROVIDE PLASMA FOR KOĀTE

The strict safety standards in place for KOĀTE manufacturing begin with the careful screening of donors at FDA-licensed plasma donation centers here in the US. To become Qualified*, donors must[6]:

+ Pass two separate medical screenings
+ Test negative for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) on two separate occasions
+ Return within 6 months to make a second donation

This means that plasma from a one-time donor, even when all viral test results are negative, will not be used to manufacture KOĀTE.

The Plasma Protein Therapeutics Association (PPTA)

Standards like the Qualified Donor requirements and NDDR are administered by the PPTA, which represents plasma therapy manufacturers and over 450 US plasma collection centers. Their voluntary standards go beyond regulatory requirements for the collection, processing and testing of human plasma. Kedrion Biopharma is Q-SEAL certified by the PPTA, which provides independent verification of adherence to these standards.[7]

IMPORTANT SAFETY INFORMATION

- Allergic reactions, including serious, life-threatening allergic reactions, are possible from the administration of antihemophilic factor preparations such as KOĀTE. 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 Important Safety Information throughout and the accompanying Full Prescribing Information.

DONATED PLASMA IS TESTED FOR VIRAL CONTAMINATION 2 DIFFERENT WAYS

2. DONATION TESTING: SEROLOGY

Serology is a process that tests donated plasma for “markers” that tell us a donor has been exposed to a virus and could pass it on to others. Donations are tested for markers to viruses such as[8,9]:

+ HIV: human immunodeficiency virus
+ HBV: hepatitis B virus
+ HCV: hepatitis C virus
+ B19V: human parvovirus B19

3. DONATION TESTING: NUCLEIC ACID AMPLIFICATION TESTING (NAT)

NAT testing detects the genetic material of viruses in plasma. NAT is very sensitive and can detect viruses before the donor has any symptoms and before markers can be detected using serology tests.[8,9]

What prevents a donor with a positive viral test result from donating at another facility?
The National Donor Deferral Registry (NDDR)

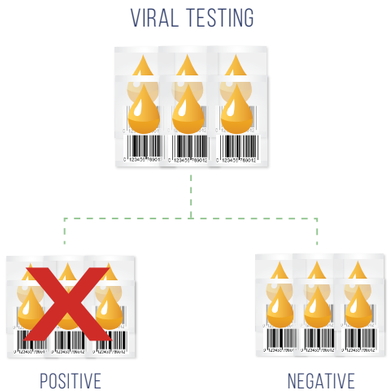
Any person who has a positive test result for HIV, HBV, or HCV at a plasma donation center is entered into this national database. These individuals are not allowed to donate plasma at any center in the US or Canada. All first-time donors are checked against the NDDR.[6]

EACH UNIT OF PLASMA IS CLOSELY TRACKED

4. PLASMA INVENTORY MANAGEMENT

As each unit of donated plasma proceeds through viral testing and manufacturing, it must be identified and tracked. Each unit of plasma receives a barcode uniquely identifying it as coming from a particular donor.

5. 60-DAY HOLD



Every unit of donated plasma is held in quarantine for at least 60 days after the donation. This allows for the identification and destruction of any plasma due to any situation such as[7]:

+ Positive viral test result
+ High-risk donor behavior
+ International travel [travel to certain countries during a time that transmission of variant Creutzfeldt-Jakob disease (vCJD) was a known risk][10]

Viral testing is done after individual donations are combined into multiple-sample pools. If any of the viral tests are positive, the contaminated sample is identified and destroyed, and the donor is traced back and placed on the NDDR.

MANUFACTURING BEGINS

6. MANUFACTURING POOL TESTING

+ Cleared plasma donations are combined into 3,000-10,000 unit manufacturing pools, which then go through another round of NAT testing.[7]
+ Manufacturing pools that pass this second round of NAT testing are cleared for further processing.

7. KOĀTE PURIFICATION

+ During manufacturing, KOĀTE is purified by separating the FVIII/VWF complex from unwanted material in the plasma.
+ These steps have also been shown to inactivate or eliminate viruses that may have remained in the manufacturing pool despite steps 1–6.[4,9]

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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.
- 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 KOĀTE are given. Your healthcare provider will monitor your levels of red blood cells and look out for signs of red blood cell breakdown.

IMPORTANT SAFETY INFORMATION

- KOĀTE 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 KOĀTE were nervousness, headache, abdominal pain (stomach ache), nausea, tingling sensation and blurred vision.

Please see Important Safety Information throughout and the accompanying Full Prescribing Information.

2 INDEPENDENT, DEDICATED VIRAL INACTIVATION STEPS

8. SOLVENT/DETERGENT TREATMENT

Viruses that have a fatty outer coat are called “enveloped” viruses. Examples of enveloped viruses include[4]:

+ HIV: human immunodeficiency virus
+ HBV: hepatitis B virus
+ HCV: hepatitis C virus
+ WNV: West Nile virus

During KOĀTE manufacturing, solvent/detergent is applied to the purified FVIII/VWF complex. This dissolves the outer coat of enveloped viruses and inactivates them. The solvent and detergent are then removed.

9. 80°C DRY HEAT TREATMENT

“Non-enveloped” viruses lack the fatty outer coat structure that surrounds enveloped viruses, and solvent/detergent treatment is not effective against them. Non-enveloped viruses include[4,9]:

+ HAV: hepatitis A virus
+ B19V: human parvovirus B19

Heat treatment has been shown to be very effective against both enveloped and non-enveloped viruses.[4,9] In the last step of manufacturing, KOĀTE is freeze-dried in its final container and then heated to 80°C (176°F) for 72 hours.

IMPORTANT SAFETY INFORMATION

- Do not use KOĀTE if you have had an allergic reaction to KOĀTE 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 KOĀTE. 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.
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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 KOĀTE are given. Your healthcare provider will monitor your levels of red blood cells and look out for signs of red blood cell breakdown.
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- 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.

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.

10. VALIDATION OF VIRAL REMOVAL

Finally, the entire manufacturing process for KOATE is “validated” to ensure that any viruses that may have entered the plasma supply despite steps 1-6 would be removed or inactivated during the manufacturing process.

Validation studies are FDA-reviewed tests that take place in a separate laboratory using a scaled-down version of the entire manufacturing process. For each manufacturing step:

1. Large amounts of virus are added to the scaled down version of product sample

2. The manufacturing step is completed

3. The resulting product is tested for the amount of virus remaining

The types of viruses included in validation studies are those of significant concern, like HIV, HAV, HBV and HCV. Sometimes, a model virus is used that is similar to the virus of concern. The results of KOĀTE’s validation studies are included in the accompanying Prescribing Information.

Please note KOĀTE is made from human blood and, therefore, still carries a risk of transmitting infectious agents, such as viruses, the agent of the variant Creutzfeldt-Jakob disease (vCJD), or unknown infectious agents.

11. PHARMACOVIGILANCE AND FOLLOW-UP

There is a process in place to diligently and intensely investigate any reports of adverse reactions associated with KOĀTE, including potential virus transmission.

There have been **ZERO** documented cases of viral transmission associated with KOĀTE’s current manufacturing process[5]

KOĀTE®
[Antihemophilic Factor (Human)]

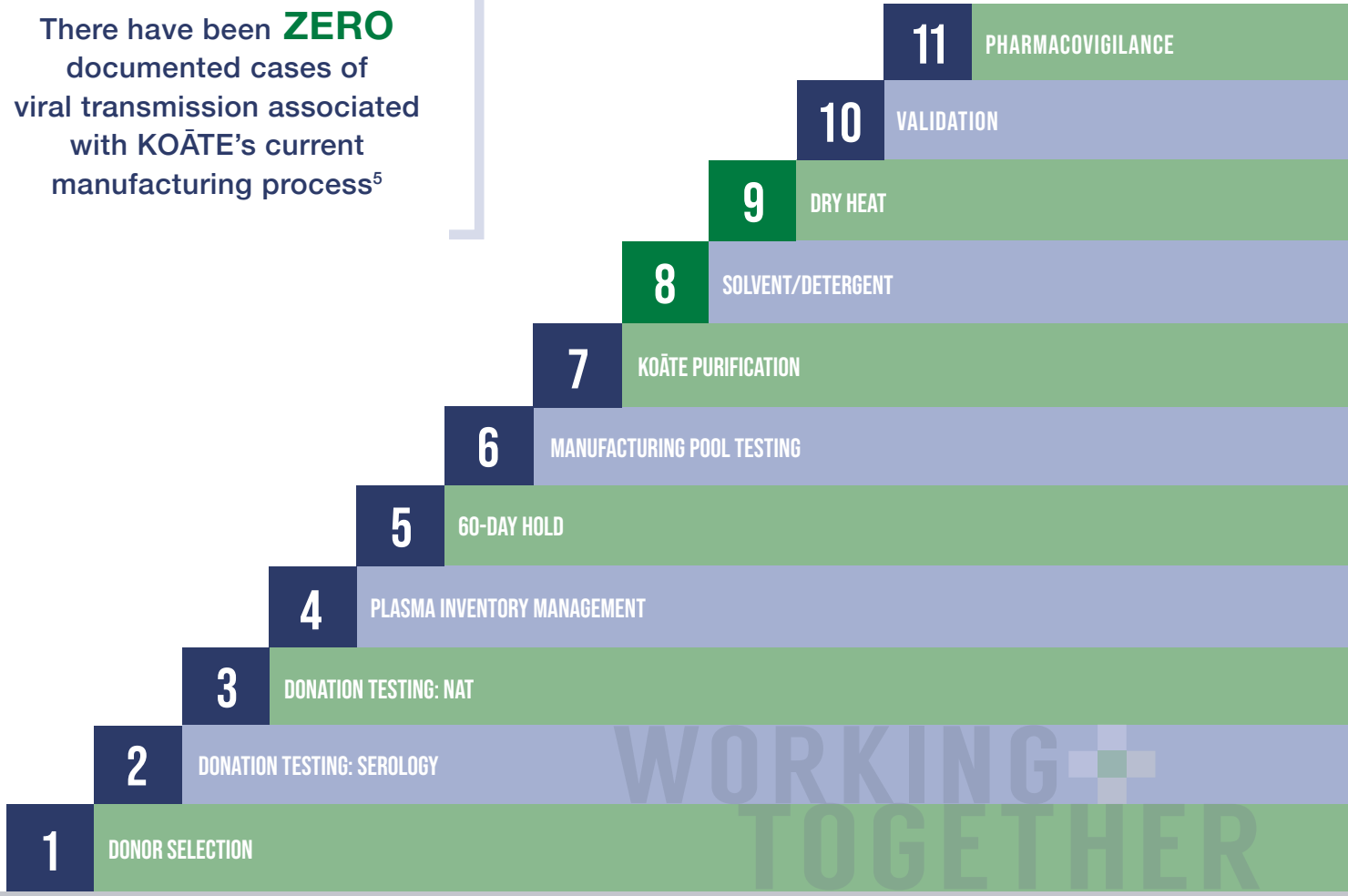
References: 1. Basics About Hemophilia. Centers for Disease Control and Prevention website. https://www.cdc.gov/ncbddd/hemophilia/facts.html. Accessed June 1, 2018. **2.** Hemophilia Treatment. Centers for Disease Control and Prevention website. https://www.cdc.gov/ncbddd/hemophilia/treatment.html. Accessed June 1, 2018. **3.** De Meyer SF, Deckmyn H, Vanhoorelbeke K. von Willebrand factor to the rescue. *Blood*. 2009;113(21):5049-57. **4.** KOĀTE [prescribing information]. Fort Lee, NJ. Kedrion Biopharma Inc. 2016. **5.** Data on File. **6.** International Quality Plasma Program (IQPP). PPTA website. https://www.pptaglobal.org/safetyquality/standards/iqpp#Donor. Accessed June 5, 2018. **7.** Quality Standards of Excellence, Assurance and Leadership (QSEAL). PPTA website. https://www.pptaglobal.org/safety-quality/standards/qseal. Accessed June 5, 2018. **8.** Pathogen Safety. PPTA website. https://www.pptaglobal.org/safety-quality/pathogen-safety. Accessed June 6, 2018. **9.** Klamroth R, Groner A, Simon TL. Pathogen inactivation and removal methods for plasma-derived clotting factor concentrates. *Transfusion*. 2014;54:1406-17. **10.** Source Plasma Full-Length PPTA Donor History Questionnaire. PPTA website. https://www.pptaglobal.org/images/dhq/2016/2_Full_Length_Directions_for_Use_V2.0_July_2016.pdf

Please see Important Safety Information throughout and the accompanying Full Prescribing Information.

STEPS TO SAFETY

KOĀTE®
[Antihemophilic Factor (Human)]

There have been **ZERO** documented cases of viral transmission associated with KOĀTE's current manufacturing process[5]



IMPORTANT SAFETY INFORMATION

- KOĀTE 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 Important Safety Information throughout and the accompanying Full Prescribing Information.

KEDRION BIOPHARMA

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KOĀTE®, 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 ----------

KOĀTE 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

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

---------- DOSAGE AND ADMINISTRATION ----------

For intravenous use after reconstitution only.

- Each vial of KOĀTE 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 KOĀTE administration is determined by the type of bleeding episode and the recommendation of the treating physician.

---------- DOSAGE FORMS AND STRENGTHS ----------

KOĀTE 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 KOĀTE or its components. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, discontinue KOĀTE 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)
- KOĀTE 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*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KOĀTE® 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

KOĀTE 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 KOĀTE 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:

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 KOĀTE 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 KOĀTE and the diluent (Sterile Water for Injection) to room temperature before use.
3. Remove the shrink band from the KOĀTE vial. Do not use KOĀTE if the shrink band is absent or shows signs of tampering, and notify Grifols Therapeutics LLC immediately.
4. Remove the plastic cap from the KOĀTE 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 KOĀTE vial upright on a flat surface, and invert the diluent vial with the Mix2Vial still attached.
10. While holding the KOĀTE 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 KOĀTE 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 KOĀTE vial, directing the stream of fluid against the wall of the vial.
11. With the diluent and KOĀTE 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 KOĀTE vial.
14. Immediately invert the system upside down and then draw the reconstituted KOĀTE 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 KOĀTE within 3 hours after reconstitution. Do not refrigerate after reconstitution.

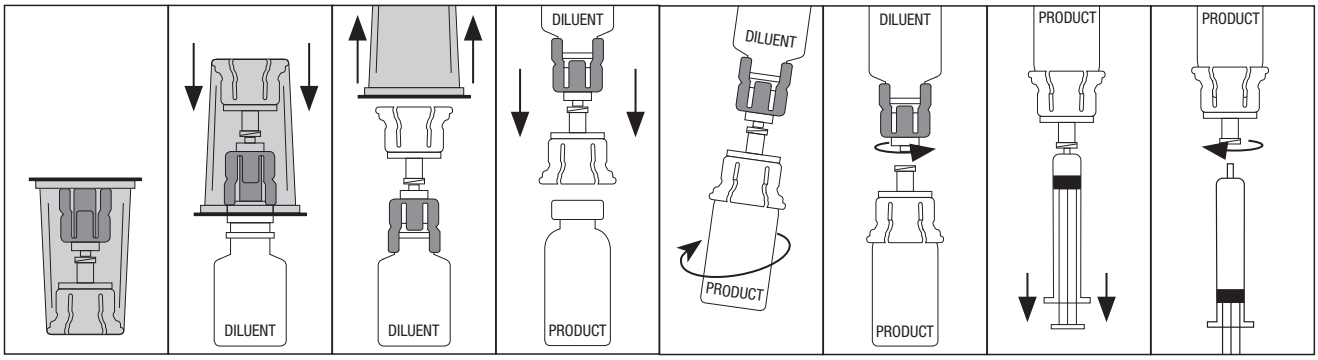


Figure 1 Figure 2 Figure 3 Figure 4 Figure 5 Figure 6 Figure 7 Figure 8

2.3 Administration

For intravenous administration only

- If the dose requires more than one vial of KOĀTE:
  - 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

KOĀTE® (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 KOĀTE vial.

4 CONTRAINDICATIONS

KOĀTE is contraindicated in patients who have had hypersensitivity reactions, including anaphylaxis, to KOĀTE 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

KOĀTE 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 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 KOĀTE and consider administering serologically compatible Type O red blood cells and providing alternative therapy.

5.4 Transmissible Infectious Agents

Because KOĀTE 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 KOĀTE. 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 KOĀTE.

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 KOĀTE 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 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 KOĀTE use in pregnant women to inform on drug-associated risk. Animal reproduction studies have not been conducted using KOĀTE. It is not known whether KOĀTE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. KOĀTE 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 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 and any potential adverse effects on the breast-fed infant from KOĀTE 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 KOĀTE 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 KOĀTE 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

KOĀTE, 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 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.

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

The KOĀTE 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 KOĀTE manufacturing process are 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 KOĀTE 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

KOĀTE 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 KOĀTE normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of KOĀTE 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. Bioequivalence of the dry heat-treated KOĀTE to the unheated KOĀTE 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 KOĀTE 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 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 3: PK Parameters of KOĀTE (Stage I of Crossover Trial)

Parameter	KOĀTE Dry Heat-treated (mean $\pm$ SD)	KOĀTE 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)	16.1 $\pm$ 3.2	16.1 $\pm$ 5.1

14 CLINICAL STUDIES

The efficacy of KOĀTE 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 with unheated KOĀTE. Nineteen subjects were randomized and received a single dose of 50 IU/kg of either heated KOĀTE 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, 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

KOĀTE 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 KOĀTE in IU is stated on each carton and vial label.

Components used in the packaging of KOĀTE 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 KOĀTE in its original package to protect it from light.
- Store the KOĀTE package at 2 to 8°C (36 to 46°F). Do not freeze.
- KOĀTE 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 KOĀTE 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 KOĀTE. Advise the patients to contact their healthcare provider for further treatment and/or assessment if they experience a lack of clinical response to KOĀTE because this may be a manifestation of an inhibitor. *[see Warnings and Precautions (5.2)]*
- Inform patients that KOĀTE is made from human plasma and may carry a risk of transmitting infectious agents. While the risk that KOĀTE 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)]*

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