Factors for Health
Comprehensive Customer Focused Care

PATIENT RESOURCE

Support for you every step of the way

GRIFOLS

Factors for Health

We focus on you so that you can focus on moving forward

If you or someone you love has been diagnosed with a bleeding disorder, you may have a lot of questions. And when it comes to questions about benefits and savings options, Factors for Health has answers.

Factors for Health provides patient-focused support for people taking ALPHANATE® (antihemophilic factor / von Willebrand factor complex [human]) or AlphaNine® SD (coagulation factor IX [human]) and their families.

Whether you're looking for help navigating the complex insurance landscape or finding ways to make treatment more affordable, we're here to talk to you one-on-one.

ENROLL TODAY!

Call 844-MY-FACTOR (693-2286)
Monday to Friday, 9 AM to 6 PM ET, excluding holidays

Or use the enclosed Factors for Health enrollment form—your healthcare provider will complete the form for you

Please see Important Safety Information on pages 12-13 and refer to accompanying full Prescribing Information for ALPHANATE and for AlphaNine SD.

Factors for Health can:

Help with prescription savings
for eligible patients and caregivers

Connect you to registered nurses
who can help answer your therapy questions over the phone

Assist with insurance claims
and benefits questions

Provide information about free trial offers
for eligible patients

Please see Important Safety Information on pages 12-13 and refer to accompanying full Prescribing Information for ALPHANATE and for AlphaNine SD.

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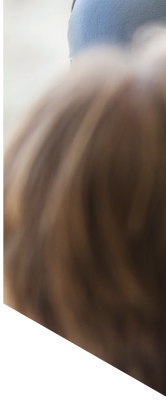

Questions about benefits?

Navigating the coverage landscape can be complex and challenging. But we can help. From investigating your current benefit guidelines to researching all your other options, Factors for Health can help you find answers—no matter what kind of insurance you have.

For patients with insurance coverage, Factors for Health can research your benefits and coverage guidelines and help coordinate communications with your insurer

For patients with no insurance coverage, or patients who experience a lapse in coverage, Factors for Health can help research alternate coverage options and assistance programs

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Monday to Friday, 9 AM to 6 PM ET, excluding holidays

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Questions about affordability?

Having all the facts about savings and affordability can help make getting and staying on treatment a little easier. You have options—and Factors for Health is here to help you find them.

- Answers to your questions from registered nurses via telephone
- Information about the Factors for Health Patient Assistance Program (PAP) to see if you qualify
- Alternate coverage options and assistance programs if you are uninsured or experience a lapse in coverage
- A free trial of ALPHANATE® (antihemophilic factor / von Willebrand factor complex [human]) or AlphaNine® SD (coagulation factor IX [human]) for patients who have never tried it before

Please see Important Safety Information on pages 12-13 and refer to accompanying full Prescribing Information for ALPHANATE and for AlphaNine SD.

$0 Copay Program

With the Factors for Health Copay Assistance Program, eligible patients or caregivers may pay **as little as $0** for prescriptions.

Program features:

- Patients receive a maximum benefit of $15,000 for eligible out-of-pocket costs in a 12-month period*
- Program helps to cover copay and coinsurance costs for ALPHANATE® (antihemophilic factor / von Willebrand factor complex [human]) or AlphaNine® SD (coagulation factor IX [human]). It does not cover costs related to physician visits and is not for inpatient use

*Individual claims exceeding $2000 will be reviewed for network eligibility. Claims that are determined to be in-network will be approved and those determined to be out-of-network may be denied by the program administrator.

†The general out-of-pocket (OOP) maximum limits for 2019 under the Affordable Care Act are $7900 (for self-only coverage) and $15,800 (for coverage other than self-only).

To be eligible, you must:

- Have commercial insurance. Patients who participate in Medicare, Medicaid, Medigap, Veterans Affairs, Department of Defense, TRICARE, or any other federal- or state-funded programs or are enrolled in a health plan that does not permit members to participate in copay assistance programs are not eligible for assistance through the program
- Have a valid prescription for ALPHANATE or AlphaNine SD
- Be a US citizen or legal resident residing within the United States or a US territory, and be under the care of a US-licensed physician with an established practice located in the United States

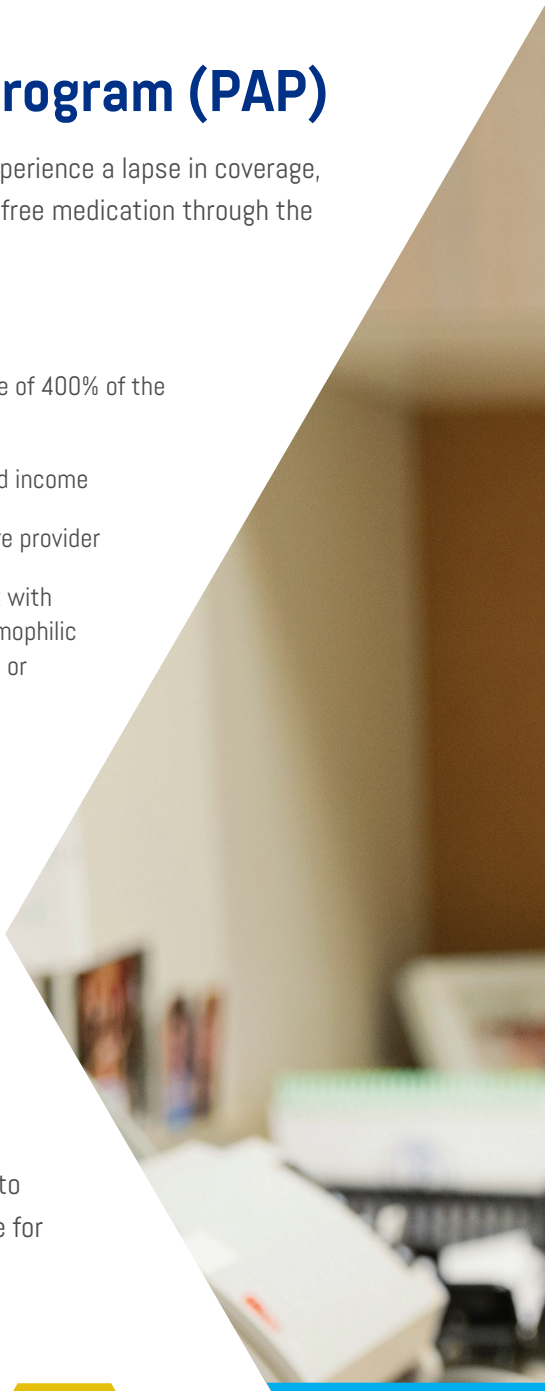
Please see Important Safety Information on pages 12-13 and refer to accompanying full Prescribing Information for ALPHANATE and for AlphaNine SD.

Patient Assistance Program (PAP)

If you have no insurance coverage, or if you experience a lapse in coverage, you may be eligible for financial assistance or free medication through the **Factors for Health PAP**.

To be eligible, you must:

- Earn an annual household adjusted gross income of 400% of the federal poverty level (FPL) or less
- Submit documentation demonstrating household income
- Provide a letter of necessity from your healthcare provider
- Have a diagnosis and dosing regimen consistent with the FDA-approved label for ALPHANATE® (antihemophilic factor / von Willebrand factor complex [human]) or AlphaNine® SD (coagulation factor IX [human])
- Be a US citizen or legal resident residing within the United States or a US territory, and be under the care of a US-licensed physician with an established practice located in the United States



Free trial offer

Patients who have never had the opportunity to try ALPHANATE or AlphaNine SD may be eligible for a free trial.

Trials include:

- Patients must not have previous experience taking ALPHANATE or AlphaNine SD
- Healthcare professional must complete form and submit with prescription information

REGISTERED NURSES ARE A PHONE CALL AWAY

Call 844-MY-FACTOR (693-2286)
to connect with a registered nurse who can help answer your questions

Please see Important Safety Information on pages 12-13 and refer to accompanying full Prescribing Information for ALPHANATE and for AlphaNine SD.

Indications for ALPHANATE® (antihemophilic factor / von Willebrand factor complex [human])

ALPHANATE is indicated for:

- Control and prevention of bleeding episodes and perioperative management in adult and pediatric patients with factor VIII (FVIII) deficiency due to hemophilia A
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (type 3) undergoing major surgery

Important Safety Information

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

Anaphylaxis and severe hypersensitivity reactions are possible with ALPHANATE. Discontinue use of ALPHANATE if hypersensitivity symptoms occur, and initiate appropriate treatment.

Development of procoagulant activity-neutralizing antibodies (inhibitors) has been detected in patients receiving FVIII-containing products. Carefully monitor patients treated with AHF products for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests.

Thromboembolic events have been reported with AHF/VWF complex (human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may occur with infusion of large doses of AHF/VWF complex (human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

Because ALPHANATE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

Monitor for development of FVIII and VWF inhibitors. Perform appropriate assays to determine if FVIII and/or VWF inhibitor(s) are present if bleeding is not controlled with expected dose of ALPHANATE.

The most frequent adverse drug reactions reported with ALPHANATE in >1% of infusions were pruritus, headache, back pain, paresthesia, respiratory distress, facial edema, pain, rash, and chills.

Please see accompanying full Prescribing Information for ALPHANATE.

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.

Indication for AlphaNine® SD (coagulation factor IX [human])

AlphaNine SD is indicated for the prevention and control of bleeding in patients with factor IX deficiency due to hemophilia B.

Important Safety Information

AlphaNine SD is made from human plasma. Plasma products carry a risk of transmitting infectious agents, including viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

Incidences of thrombosis or disseminated intravascular coagulation (DIC) have been reported following administration of factor IX complex concentrates which contain high amounts of factor II, VII, and X. AlphaNine SD contains low, nontherapeutic levels of factor II, VII, and X.

Following administration in surgery patients and individuals with known liver disease, the physician should closely observe the patient for signs and symptoms of potential disseminated intravascular coagulation.

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX products. The administration of plasma preparations may cause allergic reactions, mild chills, nausea, or stinging at the infusion site.

Nephrotic syndrome has been reported following attempted immune tolerance induction with factor IX products in hemophilia B patients with factor IX inhibitors and a history of severe allergic reactions to factor IX.

In order to minimize the possibility of thrombogenic complications, dosing guidelines should be strictly followed.

AlphaNine SD should not be administered at a rate exceeding 10 mL/minute. Rapid administration may result in vasomotor reactions.

Please see accompanying full Prescribing Information for AlphaNine SD.

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.

ENROLL TODAY!

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Monday to Friday, 9 AM to 6 PM ET, excluding holidays

Or use the enclosed Factors for Health enrollment form—
your healthcare provider will complete the form for you

All patient information is strictly confidential, and Program Staff comply with all applicable confidentiality laws. Identifiable patient health information will be used exclusively for patient support services, which may include contacting the patient's prescriber(s), prescriber office personnel, the patient's pharmacy, and the patient's insurer to provide or obtain information about health-related benefits or services. Appropriate patient consents (including opt-in support and information) and provider acknowledgments are included on the program-specific enrollment forms. Patient signature is required for the Factors for Health Patient Assistance Program.

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January 2019 US/A8/1215/0125(2)

GRIFOLS

Alphanate®

Antihemophilic Factor/
von Willebrand
Factor Complex (Human)

3051535

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])
Lyophilized Powder for Solution for Intravenous Injection
Initial U.S. Approval: 1978

----------INDICATIONS AND USAGE ----------

ALPHANATE, (antihemophilic factor/von Willebrand factor complex [human]), is indicated for:
- Control and prevention of bleeding in adult and pediatric patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

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

For intravenous injection after reconstitution only.
ALPHANATE contains the labeled amount of factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial (2).

Dose (2.1)

Treatment and Prevention of Bleeding Episodes and Excess Bleeding During and After Surgery in Patients with Hemophilia A
- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Dosing frequency determined by the type of bleeding episode and the recommendation of the treating physician.

Treatment and Prevention of Excess Bleeding During and After Surgery or Other Invasive Procedures in Patients with von Willebrand Disease
- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight.

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

ALPHANATE is available as a lyophilized powder for intravenous injection after reconstitution in single dose vials containing 250, 500, 1000, 1500 and 2000 IU FVIII (3).

----------CONTRAINDICATIONS ----------

Do not use in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components (4).

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

- Anaphylaxis and severe hypersensitivity reactions are possible. Discontinue treatment with ALPHANATE and administer appropriate emergency treatment should symptoms of anaphylaxis or severe hypersensitivity occur (5.1).
- Development of activity-neutralizing antibodies may occur in patients receiving FVIII containing products (5.2).
- Thromboembolic events (TE) may occur in VWD patients, especially with known risk factors. Monitor patients for signs and symptoms of TE (5.3).
- Intravascular hemolysis may occur with infusion of large doses of Antihemophilic Factor/von Willebrand Factor Complex. Should this condition occur and lead to progressive hemolytic anemia, discontinue administration of ALPHANATE and consider alternative therapy (5.4).
- Rapid administration may result in vasomotor reactions (5.5).
- ALPHANATE is made from human plasma and 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 (5.6).
- Perform assays to determine if FVIII inhibitors are present (5.7).

----------ADVERSE REACTIONS ----------

The most frequent adverse drug reactions reported with ALPHANATE in >1% of infusions were pruritus, headache, back pain, paresthesia, respiratory distress, facial edema, pain, rash and chills (6).

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals LLC at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- Pediatric: Age had no effect on the pharmacokinetics of ALPHANATE (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ALPHANATE, (antihemophilic factor/von Willebrand factor complex [human]), is indicated for:
- Control and prevention of bleeding episodes and perioperative management in adult and pediatric patients with Factor VIII (FVIII) deficiency due to hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease (VWD) in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

2 DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only
- Treatment with ALPHANATE should be initiated under the supervision of a physician experienced in the treatment of hemophilia.
- Each vial of ALPHANATE has the antihemophilic factor (AHF) potency (FVIII:C activity) expressed in International Units (IU) FVIII/vial on the label. Additionally, ALPHANATE contains von Willebrand Factor:Ristocetin Cofactor (VWF:RCo), which is expressed in IU VWF:RCo/vial for the treatment of VWD.

2.1 Dose

Treatment and Prevention of Bleeding Episodes and Excess Bleeding During and After Surgery in Patients with Hemophilia A
- Dosage and duration of treatment depend on the severity of the FVIII deficiency, the location and extent of bleeding, presence of inhibitors, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- Dosing requirements and frequency of dosing is calculated on the basis of an expected initial response of 2% of normal FVIII:C increase per IU FVIII:C/kg body weight administered.[1] The expected *in vivo* peak increase in FVIII level expressed as IU/dL (or % of normal) can be estimated using the following formulas:
  Dosage (international units) = body weight (kg) x desired FVIII rise (IU/dL or % normal) x 0.5 (IU/kg per IU/dL)
  or
  IU/dL (or % of normal) = [Total Dose (IU)/body weight (kg)] x 2
- Titrate dose and frequency to the patient's clinical response, including individualized needs, severity of the deficiency, severity of the hemorrhage, presence of inhibitors, and FVIII level desired. Patients may vary in their pharmacokinetic (e.g., half-life, *in vivo* recovery) and clinical responses to ALPHANATE.
- Table 1 provides dosage guidelines for the control and prevention of bleeding episodes in hemophilia A patients. Dosing should aim at maintaining a plasma factor VIII activity level at or above the plasma levels (in IU/dL or in % of normal) outlined in the table.

Table 1: Dosage Guidelines for Patients with Hemophilia A

Type of Bleeding	FVIII: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.

- Monitoring parameters:
  - Monitor plasma FVIII levels periodically to evaluate individual patient response to the dosage regimen.
  - If dosing studies have determined that a particular patient exhibits a lower/higher than expected response and shorter/longer half-life, adjust the dose and the frequency of dosing accordingly.
  - Failure to achieve the expected plasma FVIII:C level or to control bleeding after an appropriately calculated dosage may be indicative of the development of an inhibitor (an antibody to FVIII:C). Quantitate the inhibitor level by appropriate laboratory procedures and document its presence. Treatment with AHF in such cases must be individualized.[2]

Treatment and Prevention of Excess Bleeding During and After Surgery or Other Invasive Procedures in Patients with von Willebrand Disease
- The ratio of VWF:RCo to FVIII in ALPHANATE varies by lot, so with each new lot, check IU VWF:RCo/vial to ensure accurate dosing.
- Dosage and duration of treatment depend on the severity of the VWF deficiency, the location and extent of bleeding, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- The median incremental *in vivo* recoveries of VWF:RCo and FVIII:C were 3.12 (IU/dL)/(IU/kg) [mean, 3.29 ± 1.46 (IU/dL)/(IU/kg); range: 1.28 to 5.73 (IU/dL)/(IU/kg)] for VWF:RCo and 1.95 (IU/dL)/(IU/kg) [mean, 2.13 ± 0.58 (IU/dL)/(IU/kg); range: 1.33 to 3.32 (IU/dL)/(IU/kg)] for FVIII:C.
- Table 2 provides dosing guidelines for pediatric and adult patients with von Willebrand Disease.[3-6]

Table 2: Dosage Guidelines for Patients with von Willebrand Disease (Except Type 3 Subjects Undergoing Major Surgery)

Minor Surgery/Bleeding		
Parameter	**VWF:RCo**	**Target FVIII:C Activity Levels**
Pre-operative/pre-procedure dose:	**Adults:** 60 IU VWF:RCo/kg body weight. **Pediatrics:** 75 IU VWF:RCo/kg body weight.	40-50 IU/dL
Maintenance dose:	**Adults:** 40 to 60 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for 1-3 days. **Pediatrics:** 50 to 75 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for 1-3 days.	40-50 IU/dL
Therapeutic Goal (Trough)[a]:	>50 IU/dL	>50 IU/dL
Safety Monitoring:	Peak and trough at least once daily	Peak and trough at least once daily
Safety Parameter[b]:	Should not exceed 150 IU/dL	Should not exceed 150 IU/dL

Major Surgery/Bleeding		
Parameter	**VWF:RCo**	**Target FVIII:C Activity Levels**
Pre-operative/pre-procedure dose:	**Adults:** 60 IU VWF:RCo/kg body weight. **Pediatrics:** 75 IU VWF:RCo/kg body weight.	100 IU/dL
Maintenance dose:	**Adults:** 40 to 60 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for at least 3-7 days. **Pediatrics:** 50 to 75 IU VWF:RCo/kg body weight at 8 to 12 hour intervals as clinically needed for at least 3-7 days.	100 IU/dL
Therapeutic Goal (Trough)[a]:	>50 IU/dL	>50 IU/dL
Safety Monitoring:	Peak and trough at least daily	Peak and trough at least daily
Safety Parameter[b]:	Should not exceed 150 IU/dL	Should not exceed 150 IU/dL

[a] The therapeutic goal is referenced in the NHLBI Guidelines.[7]
[b] The safety parameter is extracted from Mannucci 2009.[8]

2.2 Reconstitution

1. Always use aseptic technique.
2. Ensure that concentrate (ALPHANATE) and diluent (Sterile Water for Injection, USP) are at room temperature (but not above 37 ºC) before reconstitution.
3. Remove the plastic flip off cap from the diluent vial.
4. Gently swab the exposed stopper surface with a cleansing agent such as alcohol trying to avoid leaving any excess cleansing agent on the stopper.
5. Open the Mix2Vial package by peeling away the lid (Figure 1). Leave the Mix2Vial in the clear outer packaging.
6. Place the diluent vial upright on an even surface and hold the vial tight and pick up the Mix2Vial in its clear outer packaging. Holding the diluent vial securely, push the **blue** end of the Mix2Vial vertically down through the diluent vial stopper (Figure 2).
7. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial set, ensuring the Mix2Vial remains attached to the diluent vial (Figure 3).
8. Place the product vial upright on an even surface, invert the diluent vial with the Mix2Vial attached.
9. While holding the product vial securely on a flat surface, push the **clear** end of the Mix2Vial set **vertically** down through the product vial stopper (Figure 4). The diluent will automatically transfer out of its vial into the product vial.
   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.
10. With the diluent and product vials still attached to the Mix2Vial, gently swirl the product vial to ensure the product is fully dissolved (Figure 5). Reconstitution requires less than 5 minutes. Do not shake the vial.
11. Disconnect the Mix2Vial into two separate pieces (Figure 6) by holding each vial adapter and twisting counterclockwise. After separating, discard the diluent vial with the **blue** end of the Mix2Vial.
12. Draw air into an empty, sterile syringe. Keeping the product vial upright with the **clear** end of the Mix2Vial attached, screw the disposable syringe onto the luer lock portion of the Mix2Vial device by pressing and twisting clockwise. Inject air into the product vial.
13. While keeping the syringe plunger depressed, invert the system upside down and draw the reconstituted product into the syringe by pulling the plunger back slowly (Figure 7).
14. When the reconstituted product has been transferred into the syringe, firmly hold the barrel of the syringe and the **clear** vial adapter (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial (Figure 8). Hold the syringe upright and push the plunger until no air is left in the syringe. Attach the syringe to a venipuncture set.
    NOTE: If the same patient is to receive more than one vial of concentrate, the contents of two vials may be drawn into the same syringe through a separate unused Mix2Vial set before attaching to the venipuncture set.
15. When reconstitution procedure is strictly followed, a few small particles may occasionally remain. The Mix2Vial set will remove particles and the labeled potency will not be reduced.
16. Discard all reconstitution equipment after use into the appropriate safety container. Do not reuse.
17. Use the prepared drug as soon as possible within 3 hours after reconstitution.

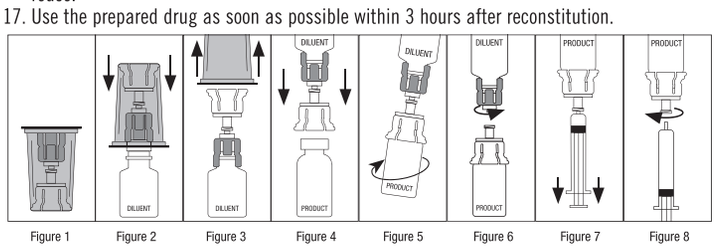

Figure 1 Figure 2 Figure 3 Figure 4 Figure 5 Figure 6 Figure 7 Figure 8

2.3 Administration

For intravenous use after reconstitution only
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Do not refrigerate after reconstitution. Store reconstituted ALPHANATE at room temperature (not to exceed 30 ºC) prior to administration, but administer intravenously within three hours.
- Use plastic disposable syringes.
- Do not administer ALPHANATE at a rate exceeding 10 mL/minute.
- Discard any unused contents into the appropriate safety container.

3 DOSAGE FORMS AND STRENGTHS

ALPHANATE is available as a lyophilized powder for intravenous injection after reconstitution. It is available in the following potencies:
250 IU FVIII/5 mL single dose vial
500 IU FVIII/5 mL single dose vial
1000 IU FVIII/10 mL single dose vial
1500 IU FVIII/10 mL single dose vial
2000 IU FVIII/10 mL single dose vial

4 CONTRAINDICATIONS

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components [see *Adverse Reactions (6)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Anaphylaxis and severe hypersensitivity reactions are possible with ALPHANATE. Early signs of allergic reactions, which can progress to anaphylaxis, may include angioedema, chest tightness, hypotension, rash, nausea, vomiting, paresthesia, restlessness, wheezing and dyspnea. Discontinue use of ALPHANATE if hypersensitivity symptoms occur, and initiate appropriate treatment.

5.2 Neutralizing Antibodies

Development of procoagulant activity-neutralizing antibodies (inhibitors) has been detected in patients receiving FVIII-containing products. Carefully monitor patients treated with AHF products for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests. No specific studies have been conducted with ALPHANATE to evaluate inhibitor formation. If expected plasma FVIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an appropriate assay that measures FVIII inhibitor concentration.

5.3 Thromboembolic Events

Thromboembolic events have been reported in von Willebrand Disease patients receiving replacement therapy with Antihemophilic Factor/von Willebrand Factor Complexes, especially in those with known risk factors for thrombosis including but not limited to elderly age, previous thrombosis, metabolic syndrome, cancer, surgery, oral contraceptive and hormone therapy, diabetes, hypertension, hyperlipidemia, smoking, and pregnancy.[9] Monitor plasma levels of VWF:RCo and FVIII activities to avoid sustained excessive VWF and FVIII activity levels (greater than 150 IU/dL), which may increase the risk of thrombotic events, during continued treatment of replacement therapy with Antihemophilic Factor/von Willebrand Factor Complexes. Consider antithrombotic measures in VWD patients at risk for thrombosis [see *Adverse Reactions (6)*].

5.4 Intravascular Hemolysis

ALPHANATE contains blood group specific isoagglutinins. Monitor the patient for signs of intravascular hemolysis and decreasing hematocrit when large and/or frequent doses of Antihemophilic Factor/von Willebrand Factor Complexes are required in patients of blood groups A, B, or AB, as cases of acute hemolytic anemia, increased bleeding tendency or hyperfibrinogenemia have been reported. These events typically subside after cessation of the factor concentrate infusion.[10] Consider alternative therapy should this condition worsen despite discontinuation of ALPHANATE.

5.5 Vasomotor Reactions

Rapid administration of a FVIII concentrate may result in vasomotor reactions. Do not administer ALPHANATE at a rate exceeding 10 mL/minute.

5.6 Transmissible Infectious Agents

Because ALPHANATE is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob Disease (vCJD) agent and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain virus infections, and by inactivating and/or removing certain viruses during manufacturing. [see *Description (11)*].

5.7 Monitoring Laboratory Tests

Monitor for development of FVIII and VWF inhibitors. Perform appropriate assays to determine if FVIII and/or VWF inhibitor(s) are present if bleeding is not controlled with expected dose of ALPHANATE.
Monitor plasma levels of VWF:RCo and FVIII activities to avoid sustained excessive VWF and FVIII activity levels (greater than 150 IU/dL), which may increase the risk of thrombotic events, particularly in patients with known risk factors.

6 ADVERSE REACTIONS

Serious adverse drug reactions (ADRs) observed in patients receiving ALPHANATE include anaphylaxis/hypersensitivity reactions. Thromboembolic events also have been observed in patients receiving ALPHANATE for VWD [see *Warnings and Precautions (5.3)*].

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse drug reaction (ADR) rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Hemophilia A
In a prospective clinical study with ALPHANATE, 23 subjects were exposed to 1217 infusions (median=42, range 2-160). The total number of exposure days was 1133, and the total number of months on study across all subjects was 234 (19.5 subject years). No ADRs or inhibitors to FVIII were reported during the study.

von Willebrand Disease
In the prospective clinical study of ALPHANATE [using both ALPHANATE Solvent Detergent (A-SD, a previous generation product) and ALPHANATE Solvent Detergent/Heat Treated (A-SD/HT, the current generation product)] in subjects with von Willebrand Disease, ADRs occurred in 5 of 36 subjects (13.9%) treated with ALPHANATE.
Sixty-one total ADRs were reported in 204 infusions. The majority of ADRs were rated as mild (55 of 61 [90.2%]). Six ADRs (9.8%) were rated as moderate. No reactions rated as serious were reported. The adverse drug reaction grading scale is defined as follows:
- Mild: the event was noted but the administration of the compound was not interrupted; the event resolved spontaneously or no treatment was required beyond administration of nonprescription analgesics.
- Moderate: the administration of the compound was not necessarily interrupted; the event required momentary treatment with prescription drugs and produced no sequelae.

Overall, the proportion of infusions associated with ADRs was 14 of 204 infusions (6.9%).
The most common ADRs reported (> 1% of infusions) were pruritus, headache, backpain, paresthesia, respiratory distress, facial edema, pain, rash, and chills.
One incident of pulmonary embolism was reported that was considered to have a possible relationship to the product. This subject received a dose of 60 IU VWF:RCo/kg body weight and the FVIII:C level achieved was 290%.
In the retrospective study conducted to determine the efficacy and safety of ALPHANATE (A-SD/HT) in a surgical or invasive procedure setting as perioperative prophylaxis against excessive bleeding, [see *Clinical Studies (14)*], 3 out of 39 subjects (7.7%) experienced 6 adverse drug reactions. Four were considered mild and 2 were considered moderate. No subject discontinued their treatment due to an adverse drug reaction. The adverse drug reactions were pruritus, paresthesia (2 events) and hemorrhage (all considered mild), and one event each of moderate hematocrit decrease and orthostatic hypotension.
One adverse drug reaction (pain) related to the treatment with heat-treated ALPHANATE (A-SD/HT) was reported in the four pediatric subjects with von Willebrand Disease during the course of the prospective study and in none of the five pediatric subjects in the retrospective clinical study.

6.2 Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
The most common post-marketing ADRs reported include allergic/hypersensitivity reactions, nausea, fever, joint pain, fatigue, and infusion site pain.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with ALPHANATE. It is also not known whether ALPHANATE can cause fetal harm when administered to a pregnant woman or affect reproductive capacity. ALPHANATE should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

No human or animal data. Use only if clearly needed.

8.3 Nursing Mothers

No human or animal data. Use only if clearly needed.

8.4 Pediatric Use

Hemophilia A
A total of 21 children (ages 7-16) were included in clinical trials with ALPHANATE. Subjects received ALPHANATE weekly for prophylaxis or suspected bleeds. They were successfully treated for 1499 bleeding episodes or as prophylaxis to prevent them (e.g. pain in the joint). The median number of units needed to treat the bleeds was 420 IU, with a range of 210 to 1620 IU. Adult and pediatric subjects did not differ in their response to treatment.
Von Willebrand Disease
The hemostatic efficacy of ALPHANATE has been studied in 20 pediatric subjects (ages 7-18) with VWD. Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo. Adult and pediatric subjects did not differ in their response to treatment.

8.5 Geriatric Use

No human or animal data. Use only if clearly needed.

11 DESCRIPTION

ALPHANATE, (antihemophilic factor/von Willebrand factor complex [human]), is a sterile, lyophilized concentrate of FVIII (AHF) and von Willebrand Factor (VWF).
ALPHANATE is prepared from pooled human plasma by cryoprecipitation of FVIII, fractional solubilization, and further purification employing heparin-coupled, cross-linked agarose which has an affinity to the heparin binding domain of VWF/FVIII:C complex. The product is treated with a mixture of tri-n-butyl phosphate (TNBP) and polysorbate 80 to inactivate enveloped viruses. The product is also subjected to an 80 ºC heat treatment step for 72 hours to inactivate enveloped and non-enveloped viruses. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products.
ALPHANATE is labeled with the antihemophilic factor potency (FVIII:C activity) in International Units (IU) FVIII/vial and with VWF:RCo activity expressed in IU VWF:RCo/vial. The activities are referenced to their respective international standards established by the World Health Organization. One IU of FVIII or one IU of VWF:RCo is approximately equal to the amount of FVIII or VWF:RCo activity in 1 mL of freshly-pooled human plasma.
ALPHANATE contains human albumin as a stabilizer, resulting in a final container concentrate with a specific activity of at least 5 FVIII:C IU/mg total protein. ALPHANATE contains no preservatives.
The composition of ALPHANATE after reconstitution is as follows:

Name of Ingredients	Nominal Composition					Units/Container
Factor VIII	250	500	1000	1500	2000	IU
von Willebrand Factor	> 400	> 400	> 400	> 400	> 400	IU per 1000 IU Factor VIII
Albumin (Human)	25	25	50	50	50	mg
Arginine	90	90	175	175	175	mg
Histidine	20	20	40	40	40	mg
Water for Injection[a]	5	5	10	10	10	mL

[a] Supplied in a separate diluent vial

Viral Reduction Capacity

The results of virus validation studies performed to determine virus reduction factors associated with several steps in the manufacturing process of ALPHANATE are summarized in **Table 3.**

In vitro inactivation studies to evaluate the solvent detergent treatment (0.3% Tri-n-butyl Phosphate and 1.0% Polysorbate 80) step in the manufacture of ALPHANATE were conducted to assess the capability of the step to inactivate enveloped viruses, such as Human Immunodeficiency viruses (HIV), as well as marker viruses such as Sindbis virus (SIN, a model for Hepatitis C virus), Vesicular Stomatitis virus (VSV, a model for large, enveloped RNA virus), Bovine Herpes virus (BHV, a model for Hepatitis B virus) and Bovine Viral Diarrhea virus (BVD, a model for Hepatitis C virus). *In vitro* inactivation studies to evaluate the dry heat treatment (80 ºC, 72 hours) step in the manufacture of ALPHANATE were conducted to assess the capability of the step to inactivate both enveloped and non-enveloped viruses, such as Hepatitis A virus (HAV), human Poliovirus Sabin type 2 (POL, a model for HAV), Canine Parvovirus (CPV, a model for Parvovirus B19), BHV and BVD. Other steps in the manufacturing process of ALPHANATE (precipitation with 3.5% polyethylene glycol (PEG), heparin affinity chromatography and lyophilization) were also evaluated for virus elimination capability using several enveloped and non-enveloped viruses as shown in **Table 3.**

Table 3: Virus Log Reduction

Virus (Model Virus for)	3.5% PEG Precipitation	Solvent-Detergent	Column Chromatography	Lyophilization	Dry Heat Cycle (80 ºC, 72 hr)	Total Log Reduction
BHV (HBV)	< 1.0	≥ 8.0	7.6	1.3	2.1	≥ 19.0
BVD (HCV)	< 1.0	≥ 4.5	< 1.0	< 1.0	≥ 4.9	≥ 9.4
POL (HAV)	3.3	–	< 1.0	3.4	≥ 2.5	≥ 9.2
CPV (B19)	1.2	–	< 1.0	< 1.0	4.1	5.3
VSV	–	≥ 4.1	–	–	–	≥ 4.1
SIN (HCV)	–	≥ 4.7	–	–	–	≥ 4.7
HIV-1	< 1.0	≥ 11.1	≥ 2.0	–	–	≥ 13.1
HIV-2	–	≥ 6.1	–	–	–	≥ 6.1
HAV	–	–	–	2.1	≥ 5.8	≥ 7.9

Additionally, the manufacturing process was investigated for its capacity to decrease infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

Several of the individual production steps in ALPHANATE manufacturing process have been shown to decrease TSE infectivity of an experimental model agent.[11] TSE reduction steps include: 3.5% polyethylene glycol precipitation (3.23 $\log_{10}$), affinity chromatography (3.50 $\log_{10}$) and saline precipitation (1.36 $\log_{10}$). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ALPHANATE contains antihemophilic factor (FVIII) and von Willebrand factor (VWF), constituents of normal plasma. FVIII is an essential cofactor in activation of factor X leading to formation of thrombin and fibrin. VWF promotes platelet aggregation and platelet adhesion on damaged vascular endothelium; it also serves as a stabilizing carrier protein for the procoagulant protein FVIII.[12, 13]

After administration, ALPHANATE temporarily replaces the missing coagulation factor VIII and von Willebrand factor needed for effective hemostasis.

12.3 Pharmacokinetics

Pharmacokinetics in Hemophilia A

Following the administration of ALPHANATE during clinical trials, the mean *in vivo* half-life of FVIII observed in 12 adult subjects with severe hemophilia A was 17.9 ± 9.6 hours. In this same study, the *in vivo* recovery was 96.7 ± 14.5% at 10 minutes post-infusion. Recovery at 10 minutes post-infusion was also determined as 2.4 ± 0.4 IU FVIII rise/dL plasma per IU FVIII infused/kg body weight.

Pharmacokinetics in von Willebrand Disease (VWD)

A pharmacokinetic crossover study was conducted in 14 non-bleeding subjects with VWD (1 type 1, 2 type 2A, and 11 type 3) comparing the pharmacokinetics of ALPHANATE (A-SD/HT) and an earlier formulation, ALPHANATE (A-SD). Subjects received, in random order at least seven days apart, a single intravenous dose of each product, 60 IU VWF:RCo/kg (75 IU VWF:RCo/kg in subjects younger than 18 years of age). Pharmacokinetic parameters were similar for the two products and indicated that they were biochemically equivalent. Pharmacokinetic analysis of ALPHANATE (A-SD/HT) in the 14 subjects revealed the following results: the median plasma levels (% normal) of VWF:RCo rose from 10 IU/dL (range: 10 to 27 IU/dL) at baseline to 206 IU/dL (range: 87 to 440 IU/dL) 15 minutes post-infusion; median plasma levels of FVIII:C rose from 5 IU/dL (range: 2 to 114 IU/dL) to 206 IU/dL (range: 110 to 421 IU/dL). The median bleeding time (BT) prior to infusion was 30 minutes (mean, 28.8 ± 4.41 minutes; range: 13.5 to 30 minutes), which shortened to 10.38 minutes (mean, 10.4 ± 3.2 minutes; range: 6 to 16 minutes) 1 hour post-infusion.

Following infusion of ALPHANATE (A-SD/HT), the median half-lives for VWF:RCo, FVIII:C and VWF:Ag were 6.91 hours (range: 3.8 to 16.22 hours), 20.92 hours (range: 7.19 to 32.2 hours), and 12.8 hours (range: 10.34 to 17.45 hours), respectively. The median incremental *in vivo* recoveries of VWF:RCo and FVIII:C were 3.12 (IU/dL)/(IU/kg) [range: 1.28 to 5.73 (IU/dL)/(IU/kg)] for VWF:RCo and 1.95 (IU/dL)/(IU/kg) [range: 1.33 to 3.32 (IU/dL)/(IU/kg)] for FVIII:C.

The pharmacokinetic data in VWD are summarized in **Table 4.**

Table 4: Pharmacokinetic data in VWD

Parameter	Plasma VWF:RCo (Mean ± SD)	Plasma FVIII:C (Mean ± SD)	Plasma VWF:Ag (Mean ± SD)
Number of patients	14	14	14
Mean plasma levels (IU/dL)			
Baseline	11.86 ± 4.97	21.00 ± 33.83	-
15 minutes post-infusion	215.50 ± 101.70	215.29 ± 94.26	-
T½ (Half-life in hours)	7.67 ± 3.32	21.58 ± 7.79	13.06 ± 2.20
Incremental *in vivo* recovery in (IU/dL)/(IU/kg)	3.29 ± 1.46	2.13 ± 0.58	-

Following infusion of both ALPHANATE (A-SD) and ALPHANATE (A-SD/HT), an increase in the size of VWF multimers was seen and persisted for at least 24 hours. The shortening of the BT was transient, lasting less than 6 hours following treatment and did not correlate with the presence of large and intermediate size VWF multimers.[14]

14 CLINICAL STUDIES

In a prospective, multi-center clinical study, 37 subjects with VWD (6 Type 1, 19 Type 2, 12 Type 3) underwent 59 surgical procedures for which ALPHANATE (A-SD) or ALPHANATE (A-SD/HT) was administered [21 subjects received ALPHANATE (A-SD), 18 received ALPHANATE (A-SD/HT), and 2 received both products] for bleeding prophylaxis (see **Table 5**). An initial pre-operative infusion of 60 IU VWF:RCo/kg (75 IU VWF:RCo/kg for subjects less than 18 years of age), was administered one hour before surgery. A blood sample was obtained 15 minutes after the initial infusion for the determination of the plasma FVIII:C level. The level had to equal or exceed 100% of normal for an operation to proceed. No cryoprecipitate or alternative FVIII product was administered during these surgical procedures. Platelets were required in two subjects. The protocol permitted intra-operative infusions of ALPHANATE (A-SD) and ALPHANATE (A-SD/HT) at 60 IU VWF:RCo/kg (75 IU VWF:RCo/kg for subjects less than 18 years of age) to be administered as required according to the judgment of the investigator.

Table 5: Number of and Types of Surgical Procedures

Parameter	Treatment with ALPHANATE		Total
Type of Surgical Procedure	A-SD	A-SD/HT	
Number of Subjects	21	18	37^
Dental	14	6	20
Dermatologic	1	1	2
Gastrointestinal	4	4	8
Gastrointestinal (diagnostic)	6	0	6
Genitourinary	0	2	2
Gynecologic	2	1	3
Head and neck	1	1	2
Orthopedic	4	3	7
Vascular	3	6	9
Total number of procedures	**35**	**24**	**59**

^ Two subjects received both preparations; the total number of subjects is therefore less than the sum of the columns.

Post-operative infusions at doses of 40 to 60 IU VWF:RCo/kg (50 to 75 IU VWF:RCo/kg for pediatric subjects) were administered at 8 to 12-hour intervals until healing had occurred. For maintenance of secondary hemostasis (after primary hemostasis was achieved), the dose was reduced after the third post-operative day [see *Dosage and Administration (2.2)*].

Overall, in the surgical procedures using either product, the BT at 30 minutes post-infusion was fully corrected in 18 (32.7%) cases, partially corrected in 24 (43.6%) cases, not corrected in 12 (21.8%) cases, and was not done in one case (1.8%). Overall, the mean blood loss was lower than predicted prospectively.

Surgical infusion summary data are included in **Table 6.**

Table 6: Prophylaxis with ALPHANATE (A-SD) and/or ALPHANATE (A-SD/HT) in Surgery

Parameter	A-SD	A-SD/HT	Total
Number of patients	21	18	37*
Number of surgical procedures	35	24	59
Median number of infusions per surgical procedure (range)	3 (1-13)	4 (1-18)	4 (1-18)
Median dosage IU VWF:RCo/kg			
Infusion #1 (range)	59.8 (19.8-75.1)	59.9 (40.6-75.0)	59.9 (19.8-75.1)
Infusion ≥ #2 combined (range)	40.0 (4.5-75.1)	40.0 (10.0-63.1)	40.0 (4.5-75.1)

* Two subjects received both products

Additionally, surgical procedures using ALPHANATE SD/HT only were categorized as major, minor or invasive procedures according to definitions used in the study. The outcome of each surgery was evaluated according to a clinical rating scale (excellent, good, poor or none) and was considered successful if the outcome was excellent or good.

Study results also were evaluated independently by two referees with clinical experience in this field in the same way (surgery categorization and outcome of each surgery according to a clinical rating scale). There was a high level of agreement between the referee evaluations and the analyzed outcome data, with a decrease of only a single success in achieving hemostasis (21/24 [referees evaluation] vs. 22/24 [investigators evaluation]).

A retrospective, multi-center study was performed to assess the efficacy of ALPHANATE (A-SD/HT) as replacement therapy in preventing excessive bleeding in subjects with congenital VWD undergoing surgical or invasive procedures, for whom DDAVP was ineffective or inadequate. A total of 61 surgeries/procedures in 39 subjects were evaluated.[15]

Of the 39 subjects, 18 had Type 1 VWD (46.2%); 12 subjects (30.8%) had Type 2 VWD, and 9 subjects (23.1%) had Type 3 VWD. Median age was 40 years; approximately one-half of the subjects were male.

The primary efficacy variable was the overall treatment outcome for each surgical or invasive procedure, as rated by the investigator using a 4-point verbal rating scale (VRS): "excellent," "good," "poor," or "none (no indication of efficacy)." The categorization of the replacement treatment outcome was based upon the investigator's clinical experience and defined in **Table 7.**

Table 7: Rating Scale and Clinical Efficacy of ALPHANATE Therapy

Rating	Clinical Efficacy*	
	Hemostasis	Dosing
Excellent	Hemostasis not different from that expected for subjects without known bleeding disorders.	No upward dosage adjustment for ALPHANATE replacement therapy.
Good	Hemostasis slightly inferior from that expected for subjects without known bleeding disorders but judged as not clinically relevant.	Minor upward dosage adjustment for ALPHANATE replacement therapy.
Poor	Less hemostasis than expected for subjects without known bleeding disorders attributed to vWD despite ALPHANATE replacement therapy.	Relevant upward dosage adjustment for ALPHANATE replacement therapy. No need for alternative therapy.
None	Severe bleeding attributed to vWD despite ALPHANATE replacement therapy.	Relevant upward dosage adjustment for ALPHANATE replacement therapy and/or need for alternative unexpected therapy.

* The efficacy assessment period included the entire perioperative period.

In addition, an independent referee committee was convened to evaluate the efficacy outcomes. More than 90% of the surgical outcomes received an investigator and referee's overall and daily rating of "effective" ("excellent" or "good") in achieving hemostasis/preventing bleeding.

The majority of ratings were considered "excellent" (≥ 81.3% in each VWD type). Nine Type 3 subjects underwent 1 major and 15 minor procedures. Two procedures (1 major and 1 minor) in 1 subject with Type 3 VWD received an overall efficacy rating of "none," and one minor procedure in a subject with Type 2 VWD received an overall efficacy rating of "poor."

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ALPHANATE is supplied in sterile, lyophilized form in a single dose vial with a vial of diluent (Sterile Water for Injection, USP) and a Mix2Vial filter transfer set. IU activity of FVIII and VWF:RCo are stated on the carton and label of each vial.

ALPHANATE is available in the following potencies and color coded based upon assay on the carton and label as follows:

Potency	NDC	Assay Color Code
250 IU FVIII/5 mL single dose vial	68516-4601-1 or 68516-4611-1	250 IU FVIII Range - grey box
500 IU FVIII/5 mL single dose vial	68516-4602-1 or 68516-4612-1	500 IU FVIII Range - blue box
1000 IU FVIII/10 mL single dose vial	68516-4603-2 or 68516-4613-2	1000 IU FVIII Range - red box
1500 IU FVIII/10 mL single dose vial	68516-4604-2 or 68516-4614-2	1500 IU FVIII Range - black box
2000 IU FVIII/10 mL single dose vial	68516-4609-2 or 68516-4615-2	2000 IU FVIII Range - green box

Storage and Handling

ALPHANATE is stable for three years, up to the expiration date printed on its label, provided that the storage temperature does not exceed 25 ºC (77 ºF). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient:

- To contact their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing [see *Warnings and Precautions (5.1)*].
- To contact their physician or treatment center for further treatment and/or assessment if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor [see *Warnings and Precautions (5.2)*].
- To contact their healthcare provider or go to the emergency department right away if a thromboembolic event should occur [see *Warnings and Precautions (5.3)*].
- That despite stringent procedures designed to reduce risk, the risk of transmitting infectious agents cannot be totally eliminated. Advise patients, especially pregnant women and immunocompromised individuals, to report any signs and symptoms of fever, rash, joint pain, or sore throat, to their physician immediately [see *Warnings and Precautions (5.6)*].

Manufactured by:
Grifols Biologicals LLC
5555 Valley Boulevard
Los Angeles, CA 90032, U.S.A.
U. S. License No. 1694

3051535

GRIFOLS

PACKAGE LEAFLET: INFORMATION FOR THE USER

Coagulation Factor IX (Human), AlphaNine® SD

Solvent Detergent Treated/Virus Filtered

3051551

DESCRIPTION

Coagulation Factor IX (Human), AlphaNine® SD, is a purified, solvent detergent treated, virus filtered preparation of Factor IX derived from human plasma.[1] It contains a minimum of 150 IU Factor IX/mg protein; levels of Factor VII (proconvertin), Factor II (prothrombin) and Factor X (Stuart-Prower Factor) which are below the limit of detection (less than 0.04 Factor VII unit, less than 0.05 Factor II unit, and less than 0.05 Factor X unit per IU Factor IX). AlphaNine SD is a sterile, lyophilized preparation intended for intravenous administration only. Each vial is a single dose container.

AlphaNine SD is labeled with the Factor IX potency expressed in International Units (IU). AlphaNine SD contains not more than (NMT) 0.04 unit of heparin, NMT 0.2 mg of dextrose, NMT 1.0 µg polysorbate 80 and NMT 0.10 µg tri(n-butyl) phosphate/IU of Factor IX. Contains no preservatives.

CLINICAL PHARMACOLOGY

AlphaNine SD is a purified formulation of Factor IX containing not less than 150 IU Factor IX activity/mg of total protein.[2] AlphaNine SD contains non-therapeutic levels of Factor II, Factor VII and Factor X.

Thrombogenicity of AlphaNine SD in animals is markedly lower than that of Factor IX Complex, Profilnine® Heat-Treated. Five lots of AlphaNine SD (three lots of non-virus filtered product and two lots of virus filtered product) failed to show any evidence of thrombogenicity when tested directly in the Wessler rabbit stasis model for thrombogenicity[3-6] at a dose of 200 IU Factor IX/kg body weight. When various lots of AlphaNine SD were further tested at doses between 300 and 650 IU Factor IX/kg, only 5 out of 40 animals (12.5%) showed evidence of thrombus formation (Wessler scores of +1, +2, +1, +1, +1 out of +4 maximum). In comparison, Factor IX Complex concentrate, Profilnine, was thrombogenic in 100% of the animals tested at a dose of 100 IU Factor IX/kg.

At a dose of 200 IU Factor IX/kg body weight in a porcine model, the heptane heat-treated formulation of this product (AlphaNine) showed little evidence of disseminated intravascular coagulation (DIC) following infusion.[7] This model exhibited no depletion of coagulation factors, a minimal increase in fibrin monomer (+1 in protamine test), a slight temporary decrease in platelet counts, and no evidence of intravascular coagulation upon gross autopsy.[8] In contrast, Harrison, et al., report that all Factor IX Complex concentrates studied in the same porcine model were thrombogenic at doses between 50 and 100 IU of Factor IX/kg animal weight.[9]

A clinical evaluation of AlphaNine SD half-life and recovery characteristics was performed. A total of 18 patients with severe to moderate hemophilia B each received a single infusion of 40 to 50 IU Factor IX/kg body weight of AlphaNine SD. Following the administration of AlphaNine SD, the mean half-life of Factor IX observed was approximately 21 hours.[2] This half-life value was computed using the biphasic linear regression model recommended by the International Society of Thrombosis and Haemostasis.[10] The half-life obtained for the solvent detergent treated product is comparable to that of AlphaNine (approximately 19 hours) as well as the range of 18 to 36 hours reported for Factor IX Complex preparations.[11] The mean recovery observed in clinical trials was approximately 48% and was comparable to that of AlphaNine (approximately 51%).[2]

A clinical trial was conducted using the heptane heat-treated product, AlphaNine, to evaluate the efficacy of the product in providing hemostatic protection during and after surgery in 13 patients with hemophilia B. The types of surgical procedures performed included bilateral knee replacement (1), total knee replacement with synovectomy (2), hip replacement (1), below the knee amputation (1), herniorrhaphy (2), hemorrhoidectomy (1), rhinoplasty (2), oral surgery (2) and Hickman catheter insertion with temporalis muscle transfer (1). Presurgery doses ranged from 30.1 to 65.0 IU Factor IX/kg; postsurgery replacement therapy doses ranged from approximately 9.4 to 52.0 IU Factor IX/kg. The number of postsurgery days of treatment ranged from 1 to 23; the number of postsurgery infusions ranged from 2 to 26. No bleeding episodes were reported and hemostasis was maintained during the course of postsurgery therapy. None of the hematologic parameters examined (hematocrit, partial thromboplastin time, prothrombin time, fibrinogen/fibrin degradation products, fibrin monomers, D-dimers and platelet counts) provided any evidence that AlphaNine possessed thrombogenic potential.[12]

A randomized crossover study with 11 hemophilia B patients was conducted with the heptane heat-treated version of the product, AlphaNine, to determine whether an infusion of AlphaNine caused less activation of the hemostatic system than the Factor IX Complex concentrate preparation, Profilnine Heat-Treated. Each subject received a single infusion of either AlphaNine or Profilnine Heat-Treated for the treatment of a bleeding episode, at a dose of 50 IU Factor IX/kg body weight. Each subject received the other Factor IX concentrate for the treatment of a subsequent bleeding episode, separated by an interval of not less than 10 days. The level of prothrombin fragment 1+2 (F_{1+2}) is a sensitive index of the cleavage of prothrombin by activated Factor X. The level of fibrinopeptide A (FPA) released into the plasma measures the activity of thrombin on fibrinogen in the formation of fibrin. Following infusion of Factor IX Complex, statistically significant increases in F_{1+2} and in FPA were detected at all monitored time points (15, 60, 90, 120 and 240 minutes postinfusion). The statistically significant elevation in these two hemostatic parameters indicates increased activation of the coagulation cascade. Administration of AlphaNine resulted in no increase in F_{1+2} at any monitored time points, and a statistically non-significant increase in FPA at 15, 60, and 90 minutes following infusion. Only at 120 and 240 minutes after infusion of AlphaNine were statistically significant increases in FPA levels detected. These results suggest that the infusion of a high purity factor IX, such as AlphaNine, may result in a lower level of activation of the coagulation cascade than does Factor IX Complex.[13]

The ability of the manufacturing process to inactivate and eliminate virus from the Coagulation Factor IX (Human) products was evaluated at key stages in the process (see Table 1). Known amounts of different viruses were added to samples obtained prior to those steps most likely to reduce virus load (DEAE Chromatography, Solvent Detergent, Dual Affinity Chromatography and nanofiltration) in the AlphaNine and AlphaNine SD processes to determine the level of viral inactivation/elimination of these specific steps in the process.

Table 1

Process Step	Virus Reduction (log_{10})							
	Sindbis	VSV	HIV-1	HIV-2	Parvo**	EMC	Reo	HAV
DEAE Chromatography	1.4	NT	NT	NT	1.5*	NT	NT	NT
Solvent-Detergent	NLT 5.3	NLT 4.9	NLT 12.2	6.0	NT	NT	NT	NT
Dual Affinity Chromatography	4.7	NT	NT	NT	2.2*	NT	NT	NT
Nanofiltration	NT	NT	NT	NT	3.6	3.4	4.1	≥ 4.4

**Porcine NT=Not tested NLT=Not less than *Lower 95% confidence interval

The retrovirus known as human immunodeficiency virus (HIV) has been identified as a causative agent of Acquired Immunodeficiency Syndrome (AIDS) and has been shown to be transmissible via blood or blood products. The solvent detergent process used in the manufacture of AlphaNine SD, was shown to inactivate greater than 12.2 logs of HIV-1 when the retrovirus was intentionally added to product samples under laboratory evaluation (as measured by virus antigen capture and reverse transcriptase assays). In addition, this process was shown to inactivate 6 logs of HIV-2 (as measured by reverse transcriptase assays) when the retrovirus was intentionally added to product samples.[2] In an on going efficacy and safety study of 26 patients, no subjects tested positive for HIV or viral hepatitis in relation to the investigation drug.[2]

In order to assess the ability of the solvent detergent treatment process to inactivate other viruses such as hepatitis B and C virus, the inactivation of the model viruses, Sindbis virus, a model virus for hepatitis C virus, and vesicular stomatitis virus (VSV), a model RNA virus for lipid enveloped viruses, by solvent detergent treatment was studied. Prior to solvent detergent treatment, samples were inoculated with a titer of either Sindbis or VSV. The results demonstrated that a minimum of 5.3 logs of Sindbis and a minimum of 4.9 logs of VSV were inactivated after 180 minutes of incubation with solvent detergent (when compared to an untreated control). It should be noted that the incubation time in the actual AlphaNine SD process is twice (360 minutes total) that used in the model virus studies.

The ability of the AlphaNine SD process to eliminate virus, by physically partitioning virus from product, was evaluated at key stages of the manufacturing process. Studies were performed using a lipid-enveloped model virus (Sindbis) and non-lipid model viruses (porcine parvovirus, encephalomyocarditis virus, and reovirus). Known amounts of these viruses were added to samples obtained from the AlphaNine SD process. The amount of virus removed at each subsequent purification step was then determined by plaque assay.

Addition of Sindbis or porcine parvovirus prior to Factor IX Complex adsorption by DEAE chromatography showed this step to eliminate 1.4 logs of Sindbis and 1.5 logs (95% confidence interval: 1.51-2.33) of added porcine parvovirus. When Sindbis or parvovirus was introduced into the process after the barium citrate precipitation step of the AlphaNine SD process, the subsequent dual affinity chromatography step was found to eliminate 4.7 logs of Sindbis and 2.2 logs (95% confidence interval: 2.25-2.75) of added parvovirus. When parvovirus, encephalomyocarditis virus (EMC), or Reovirus was introduced into the process after the dual affinity chromatography step, the subsequent nanofiltration step of the AlphaNine SD process was found to eliminate 3.6 logs of parvovirus, 3.4 logs of EMC and 4.1 logs of added Reovirus. The studies mentioned above indicate that the manufacturing process of AlphaNine SD is capable of reducing viruses by approximately 6 logs, in addition to virus reduction achieved by the solvent detergent process.[14] In another study, the nanofiltration step removed ≥ 4.4 logs of hepatitis A virus (HAV), a non-lipid enveloped virus. Table 1 summarizes the reduction factors obtained for each virus when individual steps in the manufacturing process for AlphaNine SD were validated for virus removal/inactivation.

INDICATIONS AND USAGE

AlphaNine SD is indicated for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. AlphaNine SD contains low, non-therapeutic levels of Factors II, VII, and X, and, therefore, is *not* indicated for the treatment of Factor II, VII or X deficiencies. This product is also *not* indicated for the reversal of coumarin anticoagulant-induced hemorrhage, nor in the treatment of hemophilia A patients with inhibitors to Factor VIII.

CONTRAINDICATIONS

None known.

WARNINGS

Because Coagulation Factor IX (Human), AlphaNine SD is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma to the application of viral elimination/reduction steps such as column chromatography, solvent detergent treatment and nanofiltration in the manufacturing process. Despite these measures, such product can potentially transmit disease, therefore the risk of infectious agents cannot be totally eliminated. The physician should weigh the risks and benefits of the use of this product and should discuss these with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. Scientific opinion encourages hepatitis B and hepatitis A vaccinations at birth or diagnosis for patients with hemophilia.

Incidences of thrombosis or disseminated intravascular coagulation (DIC), have been reported following administration of Factor IX Complex concentrates which contain high amounts of Factor II, VII and X.

Following administration of Coagulation Factor IX (Human), AlphaNine SD in surgery patients and individuals with known liver disease, the physician should closely observe the patient for signs or symptoms of potential disseminated intravascular coagulation (DIC). Continued administration of the product should be left to the discretion of the physician.

Allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX products. Frequently these events have occurred in close temporal association with the development of factor IX inhibitors. Patients should be informed of the early symptoms and signs of hypersensitivity reactions, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia and anaphylaxis. Patients should be advised to discontinue use of the product and contact physician and/or seek immediate emergency care, depending on the severity of the reactions, if any of these symptoms occur.

Nephrotic syndrome has been reported following attempted immune tolerance induction with factor IX products in Hemophilia B patients with factor IX inhibitors and a history of severe allergic reactions to Factor IX. The safety and efficacy of using AlphaNine SD in attempted immune tolerance induction has not been established.

In Previously Untreated Patients (PUPs), it is possible that anaphylaxis may occur after a median exposure of eleven (11) days.[15] It is recommended that these patients are monitored closely between the tenth and twentieth exposure day.

PRECAUTIONS

General

In order to minimize the possibility of thrombogenic complications, dosing guidelines should be *strictly* followed. Refer to "Dosage and Administration" section for recommended amount of product to be administered.

AlphaNine SD should *not* be administered at a rate exceeding 10 mL/minute. Rapid administration may result in vasomotor reactions.

Nursing personnel and others who administer this material should exercise appropriate caution in handling due to the risk of exposure to viral infection.

Discard any unused contents into the appropriate safety container. Discard administration equipment after single use into the appropriate safety container. Do not resterilize components.

Information for Patients

Patients should be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

Some viruses, such as parvovirus B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect sero-negative pregnant women, or immunocompromised individuals. The majority of parvovirus B19 and hepatitis A infections are acquired by environmental (natural) sources.

Preliminary information suggests a relationship may exist between the presence of major deletion mutations in the Factor IX gene and an increased risk of inhibitor formation and of acute hypersensitivity reactions. Patients known to have major deletion mutations of the Factor IX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to product.

Pregnancy Category C

Animal reproduction studies have not been conducted with AlphaNine SD. It is also not known whether AlphaNine SD can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. AlphaNine SD should be given to a pregnant woman only if clearly indicated.

Pediatric Use

Clinical trials for safety and effectiveness in pediatric patients 16 years of age and younger have not been conducted. Across a well controlled half-life and recovery clinical trial in patients previously treated with Factor IX concentrates of Hemophilia B, the three pediatric patients receiving AlphaNine SD (solvent detergent treated) responded similarly when compared with 15 adult patients.[2] In an ongoing safety and efficacy clinical trial in patients not previously treated with Factor IX concentrates for Hemophilia B, 21 pediatric patients received AlphaNine SD (solvent detergent treated) responded similarly when compared with the five adult patients above the age of 16 years. Adverse events were similar in this group compared to the patients above the age of 16 years. Anecdotal evaluation of the results indicates no safety and efficacy differences between pediatric and adult populations.

ADVERSE REACTIONS

The administration of plasma preparations may cause allergic reactions, mild chills, nausea or stinging at the infusion site. For most reactive individuals, slowing the infusion rate relieves the symptoms. For those highly reactive individuals, a different lot may be satisfactory.

Adverse reactions, characterized by either thrombosis or disseminated intravascular coagulation (DIC), have been reported following administration of Factor IX Complex concentrates. Patients who receive Coagulation Factor IX (Human), AlphaNine SD, following operation, or those with known liver disease, should be kept under close observation for potential signs or symptoms of intravascular coagulation. Continued administration should be left to the discretion of the physician.

In the clinical study that compared the *in vivo* half-life and recovery of AlphaNine SD and HT products, no adverse events were associated with 18 infusions of AlphaNine SD administered to 18 individuals with severe to moderate hemophilia B.[2] Short term safety of the earlier version of this product, AlphaNine, was demonstrated by an absence of adverse events after 225 infusions of this product were received by 31 patients participating in three clinical trials. In the clinical trial to evaluate efficacy of AlphaNine in providing hemostatic protection during and after surgery, 13 patients received a total of 370,655 IU of AlphaNine. In 208 total infusions, each patient received approximately 15,000 IU (range 3,295 to 52,200 IU Factor IX) in an average of 16 infusions (range 2 to 26 infusions). Results from this study showed no bleeding episodes during the course of postsurgery therapy. There was no hematological evidence (measured by hematocrit, partial thromboplastin time, prothrombin time, fibrinogen/fibrin degradation products, fibrin monomers, D-dimers and platelet counts) of thrombogenicity.[12]

To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION

For adult usage:

AlphaNine SD should be administered intravenously promptly following reconstitution. Administration of AlphaNine SD within three hours after reconstitution is recommended to avoid the potential ill effect of any inadvertent bacterial contamination occurring during reconstitution. Discard any unused contents into the appropriate safety container.

Each vial of AlphaNine SD is labeled with the total units expressed as International Units (IU) of Factor IX, which is referenced to the WHO International Standard. One unit approximates the activity in one mL of pooled normal human plasma.

The amount of AlphaNine SD required to establish hemostasis will vary with each patient and depend upon the circumstances. The following formula may be used as a guide in determining the number of units to be administered.[16]

Body weigth (in kg)	X	Desired increase in Plasma Factor IX (Percent)	X	1.0 IU/kg	=	Number of Factor IX IU Required
Example: 70 kg	X	40 (% increase)	X	1.0 IU/kg	=	2,800 IU AlphaNine SD

In clinical practice there is variability between patients and their clinical response. Therefore, the Factor IX level of each patient should be monitored frequently during replacement therapy.

For pediatric usage: See PRECAUTIONS

Treatment Guidelines for Hemorrhagic Events and Surgery in Patients Diagnosed with Hemophilia B

Type of Hemorrhage or Surgical Procedure	Examples	Treatment Guidelines
Minor Hemorrhages	Bruises, cuts or scrapes, uncomplicated joint hemorrhage	FIX levels should be brought to at least 20-30% (20-30 IU FIX/kg/twice daily) until hemorrhage stops and healing has been achieved (1-2 days).[17,18,19]
Moderate Hemorrhages	Nose bleeds, mouth and gum bleeds, dental extractions, hematuria	FIX levels should be brought to 25-50% (25-50 IU FIX/kg/twice daily) until healing has been achieved (2-7 days, on average).[17,18,19,20,21]
Major Hemorrhages	Joint and muscle hemorrhages (especially in the large muscles), major trauma, hematuria, intracranial and intraperitoneal bleeding	FIX levels should be brought to 50% for at least 3-5 days (30-50 IU FIX/kg/twice daily). Following this treatment period, FIX levels should be maintained at 20% (20 IU FIX/kg/twice daily) until healing has been achieved. Major hemorrhages may require treatment for up to 10 days.[17,18,19,20,21]
Surgery		Prior to surgery, FIX should be brought to 50-100% of normal (50-100 IU FIX/kg/twice daily). For the next 7 to 10 days, or until healing has been achieved, the patient should be maintained at 50-100% FIX levels (50-100 IU FIX/kg/twice daily).[17,18,19,20,21]

Dosing requirements and frequency of dosing is calculated on the basis of an initial response of 1% FIX increase achieved per IU of FIX infused per kg body weight and an average half-life for FIX of 18 hours. If dosing studies have revealed that a particular patient exhibits a lower response, the dose should be adjusted accordingly.

For pediatric usage: See PRECAUTIONS

RECONSTITUTION

Use Aseptic Technique

1. Warm diluent (Sterile Water for Injection, USP) and concentrate (AlphaNine SD) to at least room temperature (but not above 37 °C).
2. Remove the plastic flip off cap from the diluent vial.
3. Gently swab the exposed stopper surface with a cleansing agent such as alcohol trying to avoid leaving any excess cleansing agent on the stopper.
4. Open the Mix2Vial® package by peeling away the lid (Figure 1). Leave the Mix2Vial in the clear outer packaging.
5. Place the diluent vial upright on an even surface and hold the vial tight and pick up the Mix2Vial in its clear outer packaging. Holding the diluent vial securely, push the **blue** end of the Mix2Vial vertically down through the diluent vial stopper (Figure 2).
6. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial set, ensuring the Mix2Vial remains attached to the diluent vial (Figure 3).
7. Place the product vial upright on an even surface, invert the diluent vial with the Mix2Vial attached.
8. While holding the product vial securely on a flat surface, push the **clear** end of the Mix2Vial set **vertically** down through the product vial stopper (Figure 4). The diluent will automatically transfer out of its vial into the product vial. (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.)
9. With the diluent and product vials still attached to the Mix2Vial, gently swirl the product vial to ensure the product is fully dissolved (Figure 5). Reconstitution requires less than 5 minutes. Do not shake the vial.
10. Disconnect the Mix2Vial into two separate pieces (Figure 6) by holding each vial adapter and twisting counterclockwise. After separating, discard the diluent vial with the **blue** end of the Mix2Vial.
11. Draw air into an empty, sterile syringe. Keeping the product vial upright with the **clear** end of the Mix2Vial attached, screw the disposable syringe onto the luer lock portion of the Mix2Vial device by pressing and twisting clockwise. Inject air into the product vial.
12. While keeping the syringe plunger depressed, invert the system upside down and draw the reconstituted product into the syringe by pulling the plunger back slowly (Figure 7).
13. When the reconstituted product has been transferred into the syringe, firmly hold the barrel of the syringe and the clear vial adapter (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial (Figure 8). Hold the syringe upright and push the plunger until no air is left in the syringe. Attach the syringe to a venipuncture set.
14. NOTE: If the same patient is to receive more than one vial of concentrate, the contents of two vials may be drawn into the same syringe through a separate unused Mix2Vial set before attaching to the venipuncture set.
15. Use the prepared drug as soon as possible within three hours after reconstitution.
16. After reconstitution, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstitution procedure is strictly followed, a few small particles may occasionally remain. The Mix2Vial set will remove particles and the labeled potency will not be reduced.
17. Discard all administration equipment after use into the appropriate safety container. Do not reuse.

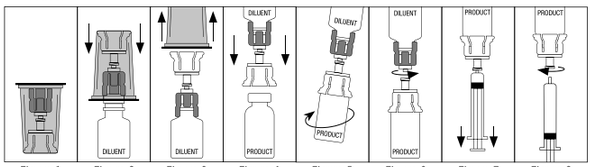

Figure 1 Figure 2 Figure 3 Figure 4 Figure 5 Figure 6 Figure 7 Figure 8

HOW SUPPLIED

AlphaNine SD is supplied in sterile, lyophilized form in single dose vials accompanied by 10 mL diluent (Sterile Water for Injection, USP). Factor IX activity, expressed in International Units (IU) which is referenced to WHO International Standard, is stated on the label of each concentrate vial. AlphaNine SD is packaged with a Mix2Vial filter transfer set for use in administration.

It is available in the following potencies, and the product is also color coded based upon assay on the carton and vial label as follows:

Potency	NDC	Assay Color Code
500 IU FIX/10 mL single dose vial	68516-3601-2 or 68516-3607-2	500 IU FIX Range - blue box
1000 IU FIX/10 mL single dose vial	68516-3602-2 or 68516-3608-2	1000 IU FIX Range - red box
1500 IU FIX/10 mL single dose vial	68516-3603-2 or 68516-3609-2	1500 IU FIX Range - black box

STORAGE

AlphaNine SD is stable for three years, up to the expiration date printed on its label, provided that the storage temperature is between 2 and 8 °C (36 and 46 °F). Do not freeze to prevent damage to diluent vial. May be stored at room temperature not to exceed 30 °C for 1 month. When removed from refrigeration, record the date removed on the space provided on the carton.

Rx only

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