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])
Sterile, lyophilized powder for injection
Initial U.S. Approval: 1978

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

Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

- Control and prevention of bleeding in patients with hemophilia A or acquired Factor VIII (FVIII) deficiency (1.1)
- 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 (1.2)

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

For Intravenous use only.
Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial (2).
Hemophilia A: Control and prevention of bleeding episodes (2.1)

- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician

von Willebrand Disease: Surgical and/or invasive procedure in adult and pediatric patients except Type 3 undergoing major surgery (2.2)

- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg/body weight at 8-12 hour intervals post-operative as clinically needed.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg/body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.
- Dosage based on protocol used in the Alphanate prospective clinical trial according to judgment of the investigator.

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

- Alphanate is a sterile, lyophilized powder for intravenous injection after reconstitution, available as 250, 500, 1000, and 1500 IU FVIII in single dose vials (3)

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

- 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. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought (5.1)
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients have been occasionally reported in the literature (5.2)
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors (5.3)
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human) (5.4)
- Rapid administration of a FVIII concentrate may result in vasomotor reactions (5.5)
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk (5.6)

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

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue (6).

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. 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)
- Labor and Delivery: No human or animal data. Use only if clearly needed (8.2)
- Nursing Mothers: No human or animal data. Use only if clearly needed (8.3)
- Pediatric Use: Clinical trials for safety and effectiveness in pediatric hemophilia A patients have not been conducted. The hemostatic efficacy of Alphanate has been studied in 20 pediatric subjects with VWD 18 years of age and under. Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo (8.4).
- Geriatric Use: No human or animal data. Use only if clearly needed (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: XX/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Hemophilia A or Acquired Factor VIII Deficiency

Alphanate®, Antihemophilic Factor/von Willebrand Factor Complex (Human), is indicated for the control and prevention of bleeding in patients with Factor VIII (FVIII) deficiency due to hemophilia A or acquired FVIII deficiency.[1]

1.2 von Willebrand Disease

Alphanate is indicated for 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 Use Only

Antihemophilic Factor (AHF) potency (FVIII:C activity) is expressed in International Units (IU) FVIII/vial on the product 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 Hemophilia A

- Treatment with Alphanate should be initiated under the supervision of a physician experienced in the treatment of hemophilia.
- 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. [2,3]

The expected *in vivo* peak increase in FVIII level expressed as IU/dL (or % normal) can be estimated using the following formulas:

Dosage (units) = body weight (kg) x desired FVIII rise (IU/dL or % normal) x 0.5 (IU/kg per IU/dL)

OR

IU/dL (or % normal) = Total Dose (IU)/body weight (kg) x 2

Thus, an administered AHF dose of 50 IU/kg will be expected to increase the circulating FVIII level to 100% of normal (100 IU/dL).

Doses administered should be titrated 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. Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests including serial FVIII activity assays be performed.

Table 1: Dosage Guidelines for the Treatment of Hemophilia A

Hemorrhagic event	Dosage (IU FVIII:C/kg Body Weight)
Minor hemorrhage: • Large Bruises • Significant cuts or scrapes • Uncomplicated joint hemorrhage	FVIII:C levels should be brought to 30% of normal (15 IU FVIII/kg twice daily) until hemorrhage stops and healing has been achieved (1–2 days).
Moderate hemorrhage: • Nose, mouth and gum bleeds • Dental extractions • Hematuria	FVIII:C levels should be brought to 50% (25 FVIII IU/kg twice daily). Treatment should continue until healing has been achieved (2–7 days, on average).
Major hemorrhage: • Joint hemorrhage • Muscle hemorrhage • Major trauma • Hematuria • Intracranial and intraperitoneal bleeding	FVIII:C levels should be brought to 80–100% for at least 3–5 days (40–50 IU FVIII/kg twice daily). Following this treatment period, FVIII levels should be maintained at 50% (25 IU FVIII/kg twice daily) until healing has been achieved. Major hemorrhages may require treatment for up to 10 days. Intracranial hemorrhages may require prophylaxis therapy for up to 6 months.
Surgery	Prior to surgery, the levels of FVIII:C should be brought to 80–100% of normal (40–50 IU FVIII/kg). For the next 7–10 days, or until healing has been achieved, the patient should be maintained at 60–100% FVIII levels (30–50 IU FVIII/kg twice daily).

Dosing requirements and frequency of dosing is calculated on the basis of an expected initial response of 2% FVIII:C increase per IU FVIII:C/kg body weight (i.e., 2% per IU/kg) and an average half-life for FVIII:C of 12 hours. If dosing studies have determined that a particular patient exhibits a lower than expected response and shorter half-life, the dose and the frequency of dosing should be adjusted 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). Its presence should be documented and the inhibitor level quantitated by appropriate laboratory procedures. Treatment with AHF in such cases must be individualized .[4-6]

Plasma FVIII levels should be monitored periodically to evaluate individual patient response to the dosage regime. Depending on the level of the inhibitor and/or clinical response, it may be appropriate to use an alternative 'bypass' therapeutic agent.

2.2 von Willebrand Disease

- Treatment with Alphanate should be initiated under the supervision of a physician experienced in the treatment of VWD.
- The ratio of VWF:RCo to FVIII in Alphanate varies by lot, so dosage should be re-evaluated whenever lot selection is changed.
- 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. Overdosage resulting in FVIII levels above 150% should be avoided.

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.[7]

The following table provides dosing guidelines for pediatric and adult patients with von Willebrand Disease. [8-11]

Table 2: Dosage Guidelines for Prophylaxis During Surgery and Invasive Procedure of von Willebrand Disease (Except Type 3 Subjects Undergoing Major Surgery)

Minor Surgery/Bleeding		
	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
Safety Monitoring:	Peak and trough at least once daily	Peak and trough at least once daily
Therapeutic Goal (Trough)[a]:	>50 IU/dL	>50 IU/dL
Safety Parameter[b]:	Should not exceed 150 IU/dL	Should not exceed 150 IU/dL

Major Surgery/Bleeding		
	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
Safety Monitoring:	Peak and trough at least daily	Peak and trough at least daily
Therapeutic Goal (Trough)[a]:	>50 IU/dL	>50 IU/dL
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.[12]

[b] The safety paramenter is extracted from Mannucci 2009.[13]

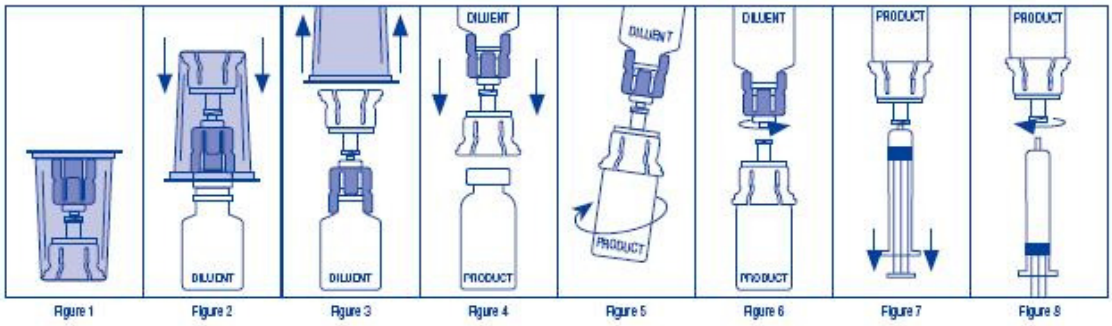
2.3 Reconstitution

Always Use Aseptic Technique

1. Warm diluent (Sterile Water for Injection, USP) and concentrate (Alphanate) 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 3 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.



2.4 Administration

Instruction for Use:

Alphanate is for intravenous use only after reconstitution. Use plastic disposable syringes. Do not refrigerate after reconstitution. Reconstituted Alphanate may be stored at room temperature (not to exceed 30 °C) prior to administration, but administer intravenously within three hours.

Discard any unused contents into the appropriate safety container.

Do not administer Alphanate at a rate exceeding 10 mL/minute.

3. DOSAGE FORMS AND STRENGTHS

Alphanate is a sterile, 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

4. CONTRAINDICATIONS

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

5. WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Severe Hypersensitivity Reactions

Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be administered.

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 studies have been conducted with Alphanate to evaluate inhibitor formation. Therefore, it is not known whether there are greater, lesser or the same risks of developing inhibitors due to the use of this product than there are with other FVIII preparations. If expected plasma FVIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay that measures FVIII inhibitor concentration should be performed. Patients with these inhibitors may not respond to treatment with Antihemophilic Factor/von Willebrand Factor Complex (Human), or the response may be much less than would otherwise be expected; therefore, larger doses of Antihemophilic Factor/von Willebrand Factor Complex (Human) are often required. The management of bleeding in patients with inhibitors requires careful monitoring, especially if surgical procedures are indicated.[4-6] Depending on the level of the inhibitor and/or clinical response, it may be appropriate to use an alternative 'bypass' therapeutic agent.

Reports in the literature suggest that patients with Type 3, severe von Willebrand Disease, may develop alloantibodies to von Willebrand factor (VWF) after replacement therapy.[14] The risk of developing alloantibodies in patients with von Willebrand disease due to the use of this product is not known.

5.3 Thromboembolic Events

Thromboembolic events have been reported in von Willebrand Disease patients receiving AHF/VWF Complex (Human) replacement therapy, especially in the setting of known risk factors for thrombosis.[15-17] In addition, endogenous high levels of FVIII have also been associated with thrombosis but no causal relationship has been established. In all VWD patients in situations of high thrombotic risk receiving coagulation factor replacement therapy, caution should be exercised and antithrombotic measures should be considered. See also *ADVERSE REACTIONS (6.1).*

5.4 Intravascular Hemolysis

Massive doses of AHF/VWF Complex (Human) have rarely resulted in acute hemolytic anemia, increased bleeding tendency or hyperfibrinogenemia.[18] Alphanate contains blood group specific isoagglutinins and, when large and/or frequent doses are required in patients of blood groups A, B, or AB, the patient should be monitored for signs of intravascular hemolysis and falling hematocrit. Should this condition occur, thus leading to progressive hemolytic anemia, the administration of serologically compatible Type O red blood cells should be considered, the administration of Alphanate should be discontinued, and alternative therapy should be considered.

5.5 Vasomotor Reactions

Rapid administration of a FVIII concentrate may result in vasomotor reactions. Alphanate should not be administered at a rate exceeding 10 mL/minute.

5.6 Transmissible Infectious Agents

Because Alphanate 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, through the application of viral elimination/reduction steps such as solvent detergent and heat treatment in the manufacturing process.[19,20] Despite these measures, such products can

still potentially transmit disease; therefore, the risk of infectious agents cannot be totally eliminated. See also *DESCRIPTION (11).*

6. ADVERSE REACTIONS

The serious adverse reaction observed in patients receiving Alphanate is anaphylaxis/hypersensitivity reactions. Thomboembolic events have also been observed in patients receiving Alphanate for VWD. See also *WARNINGS AND PRECAUTIONS (5.3).*

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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 clinical study with Alphanate, regardless of causality, 14 of 23 (60.9%) patients experienced a total of 47 adverse events. Twenty-three (48.9%) of the AEs were mild, 19 (40.4%) were moderate and 5 (10.6%) were severe.

Two of 23 (8.7%) patients experienced 10 serious AEs during the study. None of the SAEs were considered to be related to study drug.

The most common AEs were pain (combined terms), with 14 episodes occurring in 7 patients, and headache, with 3 episodes occurring in 2 patients. None of the symptoms were judged to be related to treatment (see **Table 3**).

Table 3. Most Commonly Reported AEs irrespective of relationship to study drug

Adverse Event	Number of Episodes	Number of Subjects with signs/symptoms	%
Body as a whole	**23**	**11**	**47.8%**
Pain (combined terms)	14		
Headache	3		
Accidental injury	2		
Asthenia	1		
Cellulitis	1		
Chest pain	1		
Flu syndrome	1		
Digestive system	**6**	**4**	**17.4%**
Dyspepsia	1		
GI disorder	1		
Hepatitis	1		
Nausea	1		
Tooth disorder	1		
Vomiting	1		
Respiratory system	**5**	**4**	**17.4%**
Cough increased	1		
Lung disorder	1		
Pharyngitis	1		
Respiratory disorder	1		
Rhinitis	1		
Musculoskeletal system	**3**	**3**	**13.0%**
Bone disorder	2		
Bone necrosis	1		
Skin and appendages	**3**	**3**	**13.0%**
Acne	1		
Dry skin	1		
Sweating	1		
Nervous system	**2**	**2**	**8.7%**
Insomnia	1		
Somnolence	1		
Hemic and lymphatic system	**2**	**2**	**8.7%**
Anemia	1		
Ecchymosis	1		
Urogenital system	**2**	**2**	**8.7%**
Abnormal ejaculation	1		
Cutaneous moniliasis	1		
Special senses	**1**	**1**	**4.3%**
Eye disorder	1		

VWD

In the prospective clinical study of Alphanate (A-SD/HT)** in patients with von Willebrand Disease, adverse events occurred in 18 of 36 (50.0%) subjects (irrespective of causality) and 53 of 204 (26.0%) infusions. Most of the AEs were unrelated to study drug, however, and the proportion of subjects experiencing an AE possibly, probably, or definitely related to study drug was 5 of 36 subjects (13.9%) treated with Alphanate.

The proportion of subjects with at least one serious AE, regardless of causality was 3 of 36 subjects (8.3%). There were no subjects who reported at least one serious AE possibly, probably, or definitely related to study drug.

Overall, AEs, regardless of causality, were observed in association with 53 of 204 (26.0%) infusions of Alphanate across all parts of these studies. Most AEs were unrelated to study drug, however, and the proportion of infusions associated with AEs possibly, probably, or definitely related to study drug was 14 of 204 infusions (6.9%).

The proportion of infusions associated with serious AEs, regardless of causality, was only 5 of 204 (2.5%) infusions of Alphanate. There were no observed serious AEs possibly, probably or definitely related to study drug.

**Alphanate, Solvent Detergent, non heat-treated (A-SD), is the previous formulation and Alphanate, Solvent Detergent/Heat Treated (A-SD/HT), is the current formulation. Both products are biochemically equivalent and demonstrate similar *in vivo* pharmacokinetic profiles. Both products are also similarly effective for the treatment of bleeding episodes and provide adequate hemostasis for surgical and invasive procedures, even the absence of bleeding time correction, in subjects with moderate and severe VWD.

The most common AEs regardless of causality are listed in **Table 4**.

Table 4. Most Commonly Reported AEs irrespective of relationship to study drug

Adverse Event	Number of Episodes	Number of Subjects with signs/symptoms	% of Subjects
Body as a whole	**42**	**14**	**33.3%**
Pain (combined terms)	31		
Headache	4		
Edema face	3		
Fever	2		
Digestive system	**16**	**10**	**27.8%**
Nausea	12		
Constipation	2		
Vomiting	2		
Skin and appendages	**10**	**7**	**19.4%**
Pruritis	6		
Rash	4		
Respiratory system	**4**	**2**	**5.6%**
Respiratory disorder	4		
Nervous system	**6**	**2**	**5.6%**
Paresthesia	3		
Anxiety	3		
Hemic and Lymphic system	**3**	**1**	**2.8%**
Anemia	3		

One incident of pulmonary embolus was reported that was considered to have a possible relationship to the product. This subject received the 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 peri-operative 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 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 event (pain) related to the treatment with heat-treated Alphanate (A-SD/HT) was reported on the four pediatric patients with von Willebrand Disease during the course

of the prospective study and none of the five pediatric subjects in the retrospective clinical study.[7]

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of Alphanate (A-SD/HT). 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.

Among patients treated with Alphanate (A-SD/HT), cases of allergic/hypersensitivity reactions (including urticaria, rash, pruritus, chest tightness shortness of breath, wheezing, flushing, palpitations, nausea, and vomiting) have been reported.

The following represents the most frequently reported adverse reactions: fever, chills, headache, joint pain, and fatigue. In addition, one case was reported for swelling of the parotid gland, pulmonary embolus, femoral venous thrombosis, seizure, and brief cardiorespiratory arrest.

7. DRUG INTERACTIONS

None known.

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

8.4.1 Hemophilia A Indication

Clinical trials for safety and effectiveness in pediatric hemophilia A patients 16 years of age and younger have not been conducted.

8.4.2 VWD Indication

The hemostatic efficacy of Alphanate has been studied in 20 pediatric subjects with VWD 18 years of age and under. Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo. There were no clinically important differences between pediatric patients and adults. [7]

8.5 Geriatric Use

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

11. DESCRIPTION

Alphanate 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.[22] 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 °C 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 Albumin (Human) as a stabilizer, resulting in a final container concentrate with a specific activity of at least 5 FVIII:C IU/mg total protein. Prior to the addition of the Albumin (Human) stabilizer, the specific activity is significantly higher. When reconstituted as directed, the composition of Alphanate is as follows:

Component	**Concentration**
FVIII:C activity	40 – 180 IU/mL
VWF:RCo activity	NLT 0.4 VWF:RCo IU per 1 IU of FVIII:C
Albumin (Human)	0.3 – 0.9 g/100 mL
Calcium	NMT 5 mmol/L
Glycine	NMT 750 µg per FVIII:C IU
Heparin	NMT 1.0 U/mL
Histidine	10 – 40 mmol/L
Imidazole	NMT 0.1 mg/mL
Arginine	50 – 200 mmol/L
Polyethylene Glycol and Polysorbate 80	NMT 1.0 µg per FVIII:C IU
Sodium	NMT 10 mEq/vial
Tri-n-butyl Phosphate (TNBP)	NMT 0.1 µg per FVIII:C IU

NMT = not more than
NLT = not less than

Viral Reduction Capacity

The solvent detergent treatment process has been shown by Horowitz, et al., to provide a high level of viral inactivation without compromising protein structure and function.[23] The susceptibility of human pathogenic viruses such as Human Immunodeficiency viruses (HIV), hepatitis viruses, as well as marker viruses such as Sindbis virus (SIN, a model for Hepatitis C virus) and Vesicular Stomatitis virus (VSV, a model for large, enveloped RNA virus), to inactivation by organic solvent detergent treatment has been discussed in the literature.[24]

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 demonstrated

a log inactivation of ≥ 11.1 for HIV-1, ≥ 6.1 for HIV-2, ≥ 4.1 for VSV and ≥ 4.7 for SIN. No residual virus was detected after solvent detergent treatment in any of these studies.[7]

Additional steps in the manufacturing process of Alphanate were evaluated for virus elimination capability. The dry heat cycle of 80 °C for 72 hours was shown to inactivate greater than 5.8 logs of Hepatitis A virus (HAV).[7] Precipitation with 3.5% polyethylene glycol (PEG) and heparin-actigel-ALD chromatography are additional steps studied using Bovine Herpes virus (BHV, a model for Hepatitis B virus), Bovine Viral Diarrhea virus (BVD, a second model for Hepatitis C virus), human Poliovirus Sabin type 2 (POL, a model for Hepatitis A virus), Canine Parvovirus (CPV, a model for Parvovirus B19) and HIV-1.

Table 5 summarizes the reduction factors for each virus validation study performed for the manufacturing process of Alphanate.[7]

Table 5: Virus Log Reduction

Virus (Model Virus for)	3.5% PEG Precipitation	Solvent–Detergent	Column Chromatography	Lyophilization	Dry Heat Cycle (80 °C, 72 h)	Total Log Removal
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. 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

Antihemophilic Factor/von Willebrand Factor Complex (Human) contains Antihemophilic Factor (FVIII) and von Willebrand Factor (VWF), constituents of normal plasma, which are required for clotting. The administration of Alphanate temporarily increases the plasma level of FVIII, thus minimizing the hazard of hemorrhage in patients with hemophilia A.[25,26] 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.[27,28]

12.3 Pharmacokinetics

12.3.1 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 postinfusion. 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.[7]

12.3.2 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 each of 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 [7]: the median plasma levels (% normal) of VWF:RCo rose from 10.00 IU/dL [mean, 11.86 ± 4.97 IU/dL; range: 10.00 to 27.00 IU/dL] at baseline to 206.00 IU/dL [mean, 215.50 ± 101.70 IU/dL; range: 87.00 to 440 IU/dL] 15 minutes post-infusion; median plasma levels of FVIII:C rose from 5.00 IU/dL [mean, 21.00 ± 33.83 IU/dL; range: 2.00 to 114.00 IU/dL] to 206.00 IU/dL [mean, 215.29 ± 94.26 IU/dL; range: 110.00 to 421.00 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 ± 3.20 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 (mean, 7.67 ± 3.32 hours, range, 3.80 to 16.22 hours), 20.92 hours (mean, 21.58 ± 7.79 hours; range: 7.19 to 32.20 hours), and 12.80 hours (mean, 13.06 ± 2.20 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) [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.

The pharmacokinetic data in VWD are summarized in **Table 6**.

Table 6. 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.[29]

14. CLINICAL STUDIES

VWD: Prophylaxis for Elective Surgery – Prospective Study

In a prospective, multi-center clinical study, 37 subjects with VWD (6 Type 1, 16 Type 2A, 3 Type 2B, 12 Type 3) underwent 59 surgical procedures that included 20 dental, 7 orthopedic, 8 gastrointestinal, 6 gastrointestinal (diagnostic), 9 vascular, 3 gynecologic, 2 genitourinary, 2 dermatologic and 2 head and neck procedures for which Alphanate (A-SD) or Alphanate (A-SD/HT) was administered [21 subjects were administered with Alphanate (A-SD) and 18 were administered with Alphanate (A-SD/HT), 2 received both products] for bleeding prophylaxis (see **Table 7**). Prior to each surgical procedure, the investigators provided an estimation of the expected blood loss during surgery for a normal person of the same sex and of similar stature and age as the subject undergoing the same type of surgical procedure. An initial preoperative infusion of 60 IU VWF:RCo/kg (75 IU VWF:RCo/kg for patients less than 18 years of age), was administered one hour preoperatively. A 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 only 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 patients less than 18 years of age) to be administered as required according to the judgment of the investigator.[7]

Table 7.
Number of and Types of Surgical Procedures

	Treatment with Alphanate		
Type of Surgical Procedure	A-SD	A-SD/HT	Total
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 patients received both preparations; the total number of subjects is therefore less than the sum of the columns.

Postoperative infusions at doses of 40 to 60 IU VWF:RCo/kg (50 to 75 IU VWF:RCo/kg for pediatric patients) was administered at 8- to 12-hour intervals until healing had occurred. After achieving primary hemostasis, for maintenance of secondary hemostasis the dose was reduced after the third postoperative day. See *DOSAGE AND ADMINISTRATION (2.2).*

Overall, in 55 surgical procedures undertaken with a prolonged BT pre-infusion, the BT at 30 minutes post-infusion was fully corrected in 18 (32.7%) cases, partially corrected in 24 (43.6%) cases, demonstrated no correction in 12 (21.8%) cases, and was not done in one case (1.8%).

The mean blood loss was lower than predicted prospectively. Bleeding exceeding the predicted value did not correlate with correction of the BT. Three patients had bleeding which exceeded by more than 50 mL the amount predicted prospectively. Among the latter subjects, the BT 30 minutes post-infusion was normal in one and only slightly lengthened in two cases.

Surgical infusion summary data are included in **Table 8**.

Table 8: Prophylaxis with Alphanate (A-SD) and/or Alphanate (A-SD/HT) in Surgery

	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, the surgeries 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. These outcomes are presented in **Table 9**.

Table 9.
Effect of Treatment on Surgical Prophylaxis (Investigator Evaluation): Analysis per Treated Event with Alphanate (A-SD/HT)

Investigator's Outcome Evaluation	Type of von Willebrand Disease											
	Type 1 (4 Subjects, 4 Procedures)			Type 2 (9 Subjects, 13 Procedures)			Type 3 (5 Subjects, 7 Procedures)			Total (18 Subjects, 24 Procedures)		
	Procedure			Procedure			Procedure			Procedure		
	1	2	3	1	2	3	1	2	3	1	2	3
Excellent	1	0	2	5	1	5	5	0	1	11	1	8
Good	0	0	1	0	0	1	0	0	0	0	0	2
Poor	0	0	0	0	0	0	0	0	0	0	0	0
None (no indication of efficacy)	0	0	0	0	1	0	0	1	0	0	2	0

Procedure: 1=Minor, 2=Major, 3=Invasive
Absolute frequency & proportion of successful outcomes = 22/24 (91.66%)
95% Confidence Interval (CI) for the proportion of subjects with successful prophylaxis = 0.7300 to 0.9897

The study results were also 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).

The results for the effect of treatment on surgical prophylaxis (Referee Evaluation) per treated subject are summarized in **Table 10**. There is a high level of agreement between the referee evaluations and the analyzed outcome data, with a decrease of only a single success (21/24 vs. 22/24).

Table 10.
Effect of Treatment on Surgical Prophylaxis (Referee Evaluation): Analysis per Treated Event with Alphanate (A-SD/HT)

	Referee 1	Referee 2
Number of Treated Subjects	18	18
Number of Treated Events	24	24
Success Absolute Frequency & Proportion (%)	22 (0.9166)	21 (0.8750)
* 95% CI for the Proportion	0.7300 to 0.9897	0.6763 to 0.9734

* 95% confidence interval for the proportion of subjects with successful prophylaxis, exact estimation.

VWD: Prophylaxis for Elective Surgery – Retrospective Study

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. The study was performed between September 2004 and December 2005, and 61 surgeries/procedures (in 39 subjects) were evaluated.[30]

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. The median age for subjects overall was 40 years; approximately one-half of the subjects overall 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 according to the proposed scale was based upon the investigator's clinical experience.

The secondary efficacy variables were:

- Daily (Day 0 and Day 1) treatment outcome for each surgical or invasive procedure, rated by the investigator using the same 4-point VRS used for the primary efficacy variable. Day 0 was the day of surgery, and Day 1 was the day following surgery.
- Overall treatment outcome for each surgical or invasive procedure, rated by an independent referee committee using the same 4-point VRS used for the primary efficacy variable.

In addition, an independent referee committee was convened to evaluate the efficacy outcomes. The committee was composed of 2 physicians with demonstrated clinical expertise treating subjects with similar medical characteristics to those of the study

population. The committee was blinded to the investigator ratings; and each referee evaluated the outcomes independent of one another.

More than 90% received an investigator and referee's overall and daily rating of "effective" ("excellent" or "good"). The results of the primary efficacy analysis are in **Table 11**.

Table 11. Proportion of Procedures (N = 61) With an Overall Investigator Rating of Effective versus Non-effective

Outcome of Alphanate Treatment	Proportion of Procedures (%)	95% Confidence Interval	P Value[a]
Effective[b]	95.1	87.8 – 98.6	< 0.0001
Non-effective[c]	4.9	1.4 – 12.2	

[a] Binomial test (H_0: < 70% of procedures have an overall rating of effective).
[b] Effective = Investigator rating of "excellent" or "good."
[c] Non-effective = Investigator rating of "poor" or "none."

The results of the analysis of daily investigator ratings are in **Table 12.**

Table 12. Proportion of Procedures (N = 61) With a Daily Investigator Rating of Effective versus Non-effective

Study Day[a]	Outcome of Alphanate Treatment	Proportion of Procedures (%)	95% Confidence Interval	P Value[b]
0	Effective[c]	95.1	87.8 – 98.6	< 0.0001
	Non-effective[d]	4.9	1.4 – 12.2	
1	Effective	91.8	83.5 – 96.7	< 0.0001
	Non-effective	8.2	3.3 – 16.5	

[a] Study Day 0 = day of surgery.
[b] Binomial test (H_0: < 70% of procedures have an overall rating of effective).
[c] Effective = Investigator rating of "excellent" or "good."
[d] Non-effective = Investigator rating of "poor" or "none."

The results of the analysis of overall referee ratings are in **Table 13**.

Table 13. Proportion of Procedures (N = 61) With an Overall Referee Rating of Effective versus Non-effective

Outcome of Alphanate Treatment	Proportion of Procedures (%)	95% Confidence Interval	P Value[a]
Effective[b]	91.8	83.5 – 96.7	< 0.0001
Non-effective[c]	8.2	3.3 – 16.5	

[a] Binomial test (H_0: < 70% of procedures have an overall rating of effective).

[b] Effective = Referee rating of "excellent" or "good."

[c] Non-effective = Referee rating of "poor" or "none."

The overall investigator ratings are summarized by type of VWD in **Table 14**.

Table 14. Number (%) of Investigator's Overall Efficacy Ratings by Type of VWD

Investigator's Overall Rating	Type of von Willebrand Disease							
	Type 1 (18 Subjects, 22 Procedures)		Type 2 (12 Subjects, 23 Procedures)		Type 3 (9 Subjects, 16 Procedures)		Total (39 Subjects, 61 Procedures)	
	Major	Minor[a]	Major	Minor	Major	Minor	Major	Minor
Excellent	6 (85.7%[b])	12 (80.0%)	2 (50.0%)	18 (94.7%)	0 (0.0%)	13 (86.7%)	8 (66.7%)	43 (87.8%)
Good	1 (14.3%)	3 (20.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	3 (25.0%)	4 (8.2%)
Poor	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
None (no indication of efficacy)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100)	1 (6.7%)	1 (8.3%)	1 (2.0%)

[a] Minor surgery also includes invasive procedures.

[b] % refers to percent of procedures with the given efficacy rating.

The majority of ratings were "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 1 procedure (minor) in 1 subject with Type 2 VWD received an overall efficacy rating of "poor."

The total dose of Alphanate received over the entire perioperative period of the retrospective study is summarized in **Table 15**.

Table 15: Alphanate Received (VWF:RCo) by Category of Procedure

	A-SD/HT
Number of patients	39
Number of surgical procedures	61
Mean number of infusions	5.9
Median number of infusions per surgical procedure (range)	3 (1-27)

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16. HOW SUPPLIED/STORAGE AND HANDLING

Alphanate is supplied in sterile, lyophilized form in a single dose vial with a vial of diluent (Sterile Water for Injection, USP), 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	250 IU FVIII Range - grey box
500 IU FVIII/5 mL single dose vial	68516-4602-1	500 IU FVIII Range - blue box
1000 IU FVIII/10 mL single dose vial	68516-4603-2	1000 IU FVIII Range - red box
1500 IU FVIII/10 mL single dose vial	68516-4604-2	1500 IU FVIII Range - black box

Storage

- Store under refrigeration at temperatures between 2 and 8 °C (34 to 46 °F). Do not freeze to prevent damage to diluent vial.
- May be stored at room temperature not to exceed 30 ºC for up to 2 months. If stored outside the refrigerator, record the date removed on the space provided on the carton.

17. PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reaction, including hives, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Have epinephrine available in case of severe immediate hypersensitivity reactions. If allergic symptoms occur, discontinue treatment immediately and seek emergency treatment. See *WARNINGS AND PRECAUTIONS (5.1).*
- Inform patients that inhibitors to FVIII and VWF have been detected in patients receiving FVIII or AHF/VWF Complex (Human). If expected levels are not obtained

or if bleeding is not controlled with adequate dose, contact your physician. See *WARNINGS AND PRECAUTIONS (5.2).*

- Inform patients that thromboembolic events may be associated with AHF/VWF Complex (Human). For patients with high thrombotic risk, antithrombotic measures should be considered. See *WARNINGS AND PRECAUTIONS (5.3).*
- Inform patients that despite stringent procedures designed to reduce risk, the risk of transmitting infectious agents cannot be totally eliminated. Ask 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).*

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