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GRIFOLS

Alphanate® 1000 IU

Solvent Detergent and Heat Treated

ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)

DESCRIPTION

Alphanate®, Antihemophilic Factor/von Willebrand Factor Complex (Human), a sterile, lyophilized concentrate of Factor VIII (AHF) and von Willebrand Factor (VWF), is intended for intravenous administration in the treatment of hemophilia A and von Willebrand Disease (VWD). Alphanate is prepared from pooled human plasma by cryoprecipitation of Factor VIII, 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.[1] The product is treated with a mixture of tri-n-butyl phosphate (TNBP) and polysorbate 80 to reduce the risks of transmission of viral infection. In order to provide an additional safeguard against potential non-lipid enveloped viral contaminants, the product is also subjected to an 80 °C heat treatment step for 72 hours. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products.

Alphanate is labeled with the nominal antihemophilic factor potency (FVIII:C activity) in International Units (IU) FVIII/vial. Each vial of Alphanate also contains specific labeled amount of von Willebrand Factor Ristocetin Cofactor (VWF:RCo) activity expressed in IU VWF:RCo/vial.

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 with 10 mL diluent (Sterile Water for Injection, USP), the composition of Alphanate 1000 IU is described in **Table 1.**

Table 1: Composition of Alphanate 1000 IU

Component	Concentration
Factor VIII:C	80 - 120 IU/ml
VWF:RCo	NLT 400 U/1000 FVIII:C IU
Albumin (Human)	0.3 - 0.9 g/100 mL
Calcium	NMT 5 mmol/L
Glycine	NMT 71 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.[2] 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.[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 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.

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). 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 2** summarizes the reduction factors for each virus validation study performed for the manufacturing process of Alphanate.

Table 2: Virus Log Reduction

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

CLINICAL PHARMACOLOGY

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 Factor VIII, thus minimizing the hazard of hemorrhage in patients with hemophilia A.[4,5] 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.[6,7]

Pharmacokinetics

Pharmacokinetics in Hemophilia A

Following the administration of Alphanate during clinical trials, the mean *in vivo* half-life of Factor VIII 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 10.00 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 440.00 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 3.**

Table 3. 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.[8]

INDICATIONS AND USE

Hemophilia A

Alphanate, Antihemophilic Factor/von Willebrand Factor Complex (Human), is indicated for the control and prevention of bleeding in patients with FVIII deficiency due to hemophilia A.[9]

Von Willebrand Disease

Alphanate, is also 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, except Type 3 patients undergoing major surgery.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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.

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.[10-12] 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.[13] The risk of developing alloantibodies in patients with von Willebrand disease due to the use of this product is not known.

Thromboembolic Events

Thromboembolic events have been reported in von Willebrand Disease patients receiving Antihemophilic Factor/von Willebrand Factor Complex replacement therapy, especially in the setting of known risk factors for thrombosis.[14-16] 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*.

Intravascular Hemolysis

Massive doses of AHF/VWF Complex (Human) have rarely resulted in acute hemolytic anemia, increased bleeding tendency or hyperfibrinogenemia.[17] 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.

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.

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.[18,19] Despite these measures, such products can still potentially transmit disease; therefore, the risk of infectious agents cannot be totally eliminated. See also *DESCRIPTION*.

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.
- 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.
- Inform patients that thromboembolic events may be associated with AHF/VWF Complex (Human). For patients with high thrombotic risk, antithrombotic measures should be considered.
- 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.

USE IN SPECIFIC POPULATIONS

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.

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

Hemophilia A Indication

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

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.

Geriatric Use

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

ADVERSE REACTIONS

General

Serious adverse reactions observed in patients receiving Alphanate are anaphylaxis/hypersensitivity reactions. Thromboembolic events have also been observed in patients receiving Alphanate for VWD. See also *WARNINGS AND PRECAUTIONS*.

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.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-323-225-2221.

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 4**).

Table 4. 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 5.**

Table 5. 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	**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*), 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.

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.

DOSAGE AND ADMINISTRATION

For Intravenous Use Only

Antihemophilic Factor (AHF) potency (Factor VIII:C activity) is expressed nominally in International Units (IU) 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.

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. [20,21]

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. The following dosages are presented as general guidance as shown in **Table 6.**

Table 6: Dosage Guidelines for the Treatment of Hemophilia A

Hemorrhagic event	Dosage (AHF FVIII:C IU/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 IU FVIII/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.
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 FVIII:C IU/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, the dose 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.[10-12]

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.

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.

The following **Table 7** provides dosing guidelines for pediatric and adult patients with von Willebrand Disease.[22-25]

Table 7: Dosage Guidelines for the 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[a] and trough at least daily	Peak and trough at least daily
Therapeutic Goal (Trough)[a]:	>50 IU/dL	Trough: >50 IU/dL
Safety Parameter[b]:	Should not exceed 150 IU/dL	Peak: Should not exceed 150 IU/dL

[a] The therapeutic goal is referenced in the NHLBI Guidelines.[26]
[b] The safety paramenter is extracted from Mannucci 2009.[27]

INSTRUCTIONS FOR USE AND HANDLING

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.

Do not use after the expiry date shown on the vial label.

Check assay value on label carefully before use.

Use aseptic technique during reconstitution and administration.

Left-over product must never be stored for later use, not stored in a refrigerator.

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.

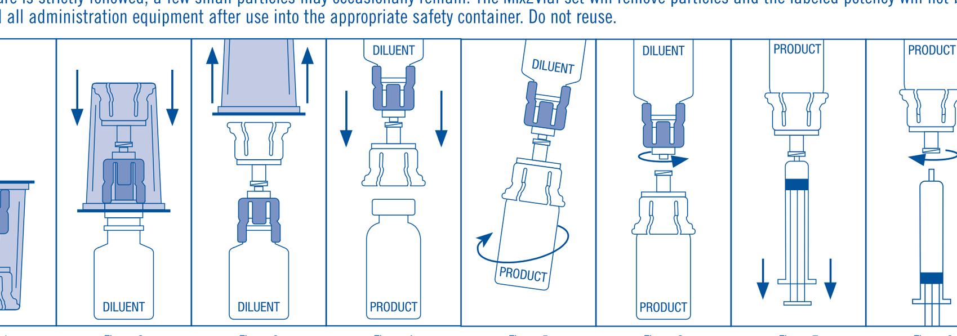

Figure 1 Figure 2 Figure 3 Figure 4 Figure 5 Figure 6 Figure 7 Figure 8

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. International unit activity of nominal Factor VIII and specific VWF:RCo are stated on the carton and label of each vial.

STORAGE

Alphanate is stable for three years, up to the expiration date printed on its label, provided that the storage temperature does not exceed 25 °C (77 °F). Do not freeze diluent.

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 8**). 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. Intra-operative infusions of A-SD and A-SD/HT at 60 IU VWF:RCo/kg (75 IU VWF:RCo/kg for patients less than 18 years of age) was administered according to the judgment of the investigator.

Table 8: Number of and Types of Surgical Procedures

	Treatment		
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*.

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 9.**

Table 9: 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 IU/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 10.**

Table 10: 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	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 11**. 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 11: 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.[28]

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 12.**

Table 12: 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 13.**

Table 13: 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 14.**

Table 14: 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 15.**

Table 15: 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	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 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 16.**

Table 16: 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)**

Rx only

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[描述]

Alphanate®，抗血友病因子/溫韋伯氏因子複合體(人來源)，為經滅菌處理的第八因子(抗血友病因子，AHF)及溫韋伯氏因子(VWF)之凍晶濃縮劑，以靜脈注射治療A型血友病及溫韋伯氏疾病(VWD)。

Alphanate是將第八因子由混合的人血漿沉澱出後，經分離溶解，利用對 VWF/FVIII:C複合體之肝素(heparin)結合部位有親合力的肝素 - agarose 交叉結合體作進一步的純化所得。本製品是以三丁基磷酸鹽(TNBP)及聚山梨醇酯八十(Polysorbate 80)混合處理，以減少病毒感染之風險。為了更進一步除去潛在的非脂套膜性病毒感染，本產品經過72小時80°C的加熱處理。不過，尚無任何步驟顯示能自凝固因子製品中完全去除病毒的感染性。

Alphanate每瓶的標籤上，FVIII:C活性以國際單位(IU)表示為IU FVIII/vial, von Willebrand Factor Ristocetin Cofactor (VWF:RCo)的活性亦以國際單位表示為IU VWF:RCo/vial。此兩者的活性分析是以世界衛生組織(WHO)所建立之國際標準品為參考基準，而一個IU大約等於每一毫升新鮮混合的人類血漿中所含有的FVIII或VWF:RCo活性。

Alphanate含有白蛋白(人來源)為安定劑，因此最終產品的比活性是每毫克總蛋白中有至少5個國際單位的FVIII:C。在未加入白蛋白(人來源)安定劑之前，此比活性是特別高。當以10 ml的稀釋劑(無菌注射用水，USP)進行稀釋後，Alphanate 1000 IU的組成如**表一**所列。

表一：Alphanate1000 IU 的組成

Component	Concentration
Factor VIII:C	80 - 120 IU/mL
VWF:RCo	NLT 400 U/1000 FVIII:C IU
Albumin (Human)	0.3 - 0.9 g/100 mL
Calcium	NMT 5 mmol/L
Glycine	NMT 71 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

[病毒減除能力]

溶劑洗滌液處理過程已被Horowitz等人證實過，可在不影響到蛋白質結構及功能之情況下將大量的病毒去活化。人類致病的病毒諸如人類免疫缺乏病毒(HIV)、肝炎病毒以及Marker病毒，如Sindbis病毒(SIN，C型肝炎病毒的模式病毒)及水泡性口炎病毒Vesicular Stomatitis Virus (VSV，大包膜RNA病毒的模式病毒)等。病毒可被有機的溶劑洗滌液處理所去活化的特性，在文獻上已曾被討論過。

為了評估在製造Alphanate時所用的溶劑洗滌液處理步驟(0.3% Tri-n-butyl phosphate and 1.0% Polysorbate 80)的試管內(in vitro)去活化研究中顯示，log去活化數量是≥ 11.1的HIV-1，≥ 6.1 的HIV-2，≥ 4.1的VSV及≥ 4.7的SIN。在這些研究中並無發現經溶劑洗滌液處理後有任何殘留病毒。

在另一個Alphanate製造過程步驟的病毒去除能力研究中，顯示了使用72小時80℃的乾燥加熱循環後可將A型肝炎病毒(HAV)去活化到大於5.8 logs。生產步驟中亦使用3.5%聚乙二醇(PEG)沉澱法和heparin-actigel-ALD色層分析法，來進行下列病毒之研究：Bovine Herpes virus (BHV, B型肝炎病毒之模式病毒)，Bovine Viral Diarrhea virus (BVD，C型肝炎病毒的第二種模式病毒)，human Poliovirus Sabin type 2 (POL, A 型肝炎病毒的模式病毒), Canine Parvovirus (CPV，微小病毒B19的模式病毒)和HIV-1。**表二**為對於每一病毒進行Alphanate製程之病毒清除確效研究的病毒降低值。

表二：病毒降低值(Virus Log Reduction)

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

此外，於製造過程中亦研究其減少傳染性海綿狀腦病(TSE)試驗製劑感染力之能力，以作為降低vCJD及CJD感染之參考。

Alphanate製造過程之幾個步驟已顯示出對於試驗模式物質可減少TSE感染力，而 TSE減少步驟包括：3.5% polyethylene glycol 沉澱 (3.23 $\log_{10}$)，親和性純化管柱 (3.50 $\log_{10}$) and saline沉澱(1.36 $\log_{10}$)。這些研究合理說明若起始物料存有低程度之CJD/vCJD感染物質，其感染力將會被去除。

[臨床的藥理學]

作用機轉

抗血友病因子／溫韋伯氏因子複合體(人來源)所含之抗血友病因子(FVIII)及von Willebrand Factor (VWF)是正常血漿的成分，是血液凝固所必需的。投予Alphanate可暫時增加血漿中第八因子的含量，因而減少A型血友病病患出血的危險性。第八因子是活化第九因子的必要輔助因子，進而形成thrombin及fibrin。VWF促進血小板凝集及血小板黏附於受傷血管內皮，它也可作為第八因子前驅凝固蛋白之穩定載體蛋白。

藥物動力學

<A型血友病之藥物動力學>

繼臨床實驗中Alphanate的投予後，12個患有嚴重A型血友病的成人受試者，其第八因子的平均體內半衰期是17.9 ± 9.6小時。在同一項研究中，輸注10分鐘後得體內重現率是96.7 ± 14.5%。輸注10分鐘後的重現率，每公斤體重所輸注的每國際單位第八因子，是每dL血漿增加第八因子2.4 ± 0.4國際單位。

<溫韋伯氏疾病(VWD)之藥物動力學>

在一個14位非出血性的VWD受試者(1位type 1、2位type 2A及11位type 3)的藥物動力學交叉研究中，比較投予Alphanate (A-SD/HT)與Alphanate® SD (A-SD)之藥物動力學。受試者以間隔至少七天之隨機投予順序，各投予單一靜脈劑量60 IU VWF:RCo/kg (受試者年齡低於18歲則投予75 IU VWF:RCo/kg)。二種產品之藥物動力學參數結果相似並顯示出生物化學相等性。在14位受試者的Alphanate (A-SD/HT)藥物動力學分析中顯示以下結果：輸注後15分鐘，VWF:RCo 的中位數血漿含量(% normal)自 baseline10.00 IU/dL [mean, 11.86 ± 4.97 IU/dL; range: 10.00 to 27.00 IU/dL] 上升至 206.00 IU/dL [mean, 15.50 ± 101.70 IU/dL; range: 87.00 to 440.00 IU/dL]；FVIII:C 的中位數血漿含量自 5.00 IU/dL [mean, 21.00 ± 33.83 IU/dL; range: 2.00 to 114.00 IU/dL]上升至 206.00 IU/dL [mean, 15.29 ± 94.26 IU/dL; range: 110.00 to 421.00 IU/dL]。輸注前的中位數出血時間(BT)是30分鐘(mean, 28.8 ± 4.41 minutes; range: 13.5 to 30 minutes)，輸注1小時後則縮短為10.38分鐘(mean, 10.4 ± 3.20 minutes; range: 6 to 16 minutes)。

輸注Alphanate (A-SD/HT)後，VWF:RCo、FVIII:C及VWF:Ag的中位數半衰期各為6.91小時(mean, 7.67 ± 3.32 hours, range: 3.80 to 16.22 hours)、20.92小時(mean, 21.58 ± 7.79 hours; range: 7.19 to 32.20 hours)及12.8小時(mean, 13.06 ± 2.20 hours; range: 10.34 to 17.45 hours)。中位數增加的 VWF:RCo及FVIII:C體內再現率各為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)]，及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)]。

VWD藥物動力學資料摘要於**表三**。

表三：VWD藥物動力學資料

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	–

輸注二種Alphanate (A-SD)及Alphanate (A-SD/HT)後，可發現VWF multimers的大小增加並持續至少24小時。出血時間(BT)的縮短是暫時性的，只持續於治療後6小時內，並且與大型及中型的VWF multimers存在無關連性。

[適應症]

A型血友病。

DDAVP®治療無效或禁忌之VWD病人在實施手術及/或侵入性治療時使用，但不適合使用於進行重度手術的Type 3病患。

[使用禁忌]

若病患對於此產品或其成份曾發生生命威脅之立即性過敏反應，包括過敏性休克(anaphylaxis)，Alphanate應禁止使用。

[警語及注意事項]

<過敏性休克及嚴重過敏反應>

由於可能發生過敏性休克及嚴重過敏反應，若這些症狀出現時，應立即停止Alphanate之治療並給予緊急治療。

<中和性抗體>

由於曾發現使用含有第八因子產品之病患發生先趨凝固物質活性—中和性抗體 (抑制物) 現象。須藉由適當之臨床觀察及實驗室檢驗來小心地監測使用抗血友病因子產品治療而發生第八因子抑制物之病患。目前醫界尚未進行研究以評估Alphanate對抑制物的產生。因此，與其他第八因子產品比較，因使用本製品而產生抑制物的危險性是更多、更少或一樣，就不得而知。如果預期的血漿第八因子活性程度未到達，或使用適當的劑量仍無法控制出血，則應分析測量第八因子抑制物濃度。含有抑制物之病患可能無法對抗血友病因子 / 溫韋伯氏因子複合體 (人來源) 之治療有反應，或者反應低於預期，因此通常需要更高劑量的抗血友病因子 / 溫韋伯氏因子複合體 (人來源)。在為含有抑制物的患者處理出血的時候必需小心的監測，特別是當需要進行手術的時候。依據抑制物程度及 / 或臨床反應，可能使用替代性繞道(bypass)治療製劑是合適的。

根據文獻報告顯示患有Type 3嚴重溫韋伯氏疾病(VWD)之病人於替換治療後可能會對溫韋伯氏因子發生異體抗體(alloantibodies)。使用本產品之溫韋伯氏疾病(VWD)病人發生異體抗體之風險性則未明。

<血栓栓塞現象>

曾有報告顯示溫韋伯氏疾病(VWD)病患施以抗血友病因子／溫韋伯氏因子複合體替代療法後出現血栓栓塞現象，特別是已知有血栓風險背景的病患。此外，內生性第八因子數值高者與血栓形成有關連性但目前並無確定的因果關係。所有VWD病患在接受凝固因子替代療法且存在高血栓風險情形時，應特別謹慎並且考量抗血栓措施。請參見[不良反應]。

<血管內溶血>

大劑量的抗血友病因子／溫韋伯氏因子複合體 (人來源) 很少會導致急性溶血性貧血，或造成大量出血之趨勢，或高血纖維蛋白原血症(hyperfibrinogenemia)。Alphanate含有特定血型的同種凝集素(isoagglutinins)，因此當A、B或AB血型的患者需要大劑量和／或多次投予時，必須監測患者是否有血管內溶血現象(intravascular hemolysis)和血球容積比(hematocrit)降低現象。若有此狀況而導致進行性的溶血性貧血，則應當考慮投予血清相容的O型紅血球，停止Alphanate投予並考慮採取其他替代方式治療。

<血管舒縮反應>

快速投予第八因子濃縮劑可能導致血管舒縮反應(vasomotor reactions)。Alphanate投予速度不應大於10 mL/minute。

<傳染性感染因子>

由於Alphanate是由混合的人類血漿製造而成，可能有傳播病毒等感染因子，以及在理論上有傳播庫賈氏症(CJD)病原因子的危險。本製劑的製造過程採用嚴密的步驟，以降低傳染一些外來的致病物質；從血漿捐贈者的篩檢，血漿的收集和檢測，和一些去除／減少病毒的步驟；例如：於製造過程中加熱和溶劑洗滌液處理。雖然經過這些處理，但是像這一類產品仍有傳染疾病的可能，也就是感染物質的危險性無法完全排除。請參見[描述]。

<病患諮詢資訊>

告訴病人過敏反應的初期徵狀，包括：蕁麻疹、全身蕁麻疹、胸部緊繃、呼吸困難、喘鳴聲、昏厥、低血壓和過敏性休克。若嚴重立即性過敏反應狀況發生時應備有可供使用之腎上腺素(epinephrine)。如果過敏反應的症狀發生，立即停止給藥並急診治療。

- **告訴病人曾發現使用含有第八因子或抗血友病因子／溫韋伯氏因子複合體 (人來源) 之病患發生FVIII及VWF抑制物。如果以適當劑量仍無法達到預期數值或無法控制出血，請與您的醫師聯絡。**
- **告訴病人血栓栓塞事件可能與抗血友病因子／溫韋伯氏因子複合體 (人來源) 相關。具有高血栓風險之病患應考量抗血栓措施。**
- **告訴病人儘管嚴格的程序設計以降低風險，傳染性感染因子的風險仍無法完全排除。要求病人，特別是懷孕婦女及免疫力不全之個人，若有任何發燒、皮疹、關節疼痛或喉嚨痛之表徵及症狀應立即向他們的醫師報告。**

[特定族群使用]

<懷孕>

C類妊娠用藥。醫界尚未對Alphanate進行過動物生殖之研究。因此，投藥給懷孕婦女是否會造成胎兒受損或影響婦女的生殖能力，即不得而知。只有在確實必要的情況下才能讓懷孕的婦女使用。

<分娩>

尚無人體及動物之研究資料。只有在確實必要的情況下才能使用。

<哺乳婦女>

尚無人體及動物之研究資料。只有在確實必要的情況下才能使用。

<孩童的使用>

[A型血友病]

尚未進行過16歲或更小兒童的安全或效果的臨床測試。

[溫韋伯氏疾病(VWD)]

曾有20位小於十八歲之患有溫韋伯氏疾病(VWD)孩童受試者以Alphanate治療止血之臨床研究。由這些受試者資料顯示，年齡並不會影響VWF:RCo之藥物動力學。孩童病患及成人於臨床上並無重大明顯的不同。

<老年人的使用>

尚無人體及動物之研究資料。只有在確實必要的情況下才能使用。

[不良反應]

<一般>

以Alphanate治療之病患之觀察到的嚴重不良反應為過敏性休克／過敏性反應。以Alphanate治療VWD之病患也被觀察到血栓栓塞現象。請參見[警語及注意事項]。

以Alphanate治療最常被報告之不良反應(> 5%)為呼吸困難、皮膚搔癢、皮疹、蕁麻疹、臉部浮腫、感覺異常、疼痛、發燒、畏寒、關節疼痛和疲勞。若發現疑似不良反應，請通知製造廠Grifols，電話：1-323-225-2221。

<臨床研究經驗>

由於執行臨床研究之狀況廣泛不同，一項藥品臨床研究中所觀察到的不良事件發生率並不能直接對比到另一項藥品臨床研究的發生率，並且可能無法充分反應臨床使用上觀察到之發生率。

• A型血友病

在一項Alphanate的臨床研究中，不論因果關係，23位病患中的14位(60.9%)經歷共47個不良事件。23個不良事件為輕度(48.9%)、19個為中度(40.4%)及5個為重度(10.6%)。

23位病患中的2位(8.7%)於研究中經歷10個嚴重不良事件。沒有一個嚴重不良事件被認為與研究藥品相關。

最常見的不良事件為疼痛(合併計算)，14個事件發生於7位病患；頭痛，3個事件發生於2位病患。沒有一個症狀被判定與治療相關。(請見表四)。

表四：不論與研究藥品之關連性而常被報告之不良事件。

不良事件	事件數量	具有表徵/症狀之受試者數量	%
全身	**23**	**11**	**47.8%**
疼痛(合併計算)	14		
頭痛	3		
意外傷害	2		
虛弱	1		
蜂窩性組織炎	1		
胸痛	1		
感冒症狀	1		
消化系統	**6**	**4**	**17.4%**
消化不良	1		
消化道疾病	1		
肝炎	1		
噁心	1		
牙齒疾病	1		
嘔吐	1		
呼吸系統	**5**	**4**	**17.4%**
咳嗽增加	1		
肺部疾病	1		
咽頭炎	1		
呼吸疾病	1		
鼻炎	1		
肌肉骨骼系統	**3**	**3**	**13.0%**
骨骼疾病	2		
骨骼壞死	1		
皮膚及其附屬器官	**3**	**3**	**13.0%**
痤瘡	1		
皮膚乾燥	1		
出汗	1		
神經系統	**2**	**2**	**8.7%**
失眠	1		
嗜睡	1		
造血及淋巴系統	**2**	**2**	**8.7%**
貧血	1		
瘀血	1		
泌尿生殖系統	**2**	**2**	**8.7%**
射精異常	1		
皮膚念珠菌病	1		
特殊感覺	**1**	**1**	**4.3%**
眼部疾病	1		

• 溫韋伯氏疾病(VWD)

在Alphanate (A-SD/HT)治療溫韋伯氏疾病(VWD)病患之前瞻性臨床研究，36位受試者中有18位(50.0%)及204次輸注中有53次(26.0%)曾發生不良事件 (不論因果關係)。大部份的不良事件都與研究藥品無關連性，但是受試者以Alphanate治療而發生不良事件之也許(possibly)、可能(probably)、或確定(definitely)與研究藥品關連之比例為36位受試者中有5位(13.9%)。**

不論因果關係，至少一次嚴重不良事件之受試者比例為36位受試者中有3位(8.3%)。在這些被通報至少一次嚴重不良事件之受試者中，並無也許(possibly)、可能(probably)、或確定(definitely)與研究藥品關連。

整體而言，不論因果關係，所有這些研究與Alphanate輸注相關之觀察到的不良事件204次中有53次(26.0%)。大部份的不良事件都與研究藥品無關連性，但是輸注引起之不良事件之也許(possibly)、可能(probably)、或確定(definitely)與研究藥品關連之比例為204次中有14次(6.9%)。不論因果關係，Alphanate輸注引起之嚴重不良事件之比例為204次中有5次(2.5%)。在這些被觀察通報之嚴重不良事件中，並無也許(possibly)、可能(probably)、或確定(definitely)與研究藥品關連。

****Alphanate (A-SD)，僅以溶劑洗滌液而未經熱處理，是Alphanate之前一製劑產品。Alphanate (A-SD/HT)，以溶劑洗滌液及經熱處理，是Alphanate目前之製劑產品。二項產品是生物化學性相等並且顯示相似的體內藥物動力學特性。二項產品對於治療出血事件是同樣有效，並且對於中度及重度VWD受試者，即使在沒有出血時間校正狀況下，也可以提供外科手術及侵入性手術足夠的止血作用。**

不論與研究藥品之關連性而常被報告之不良事件，請見表五。

表五：不論與研究藥品之關連性而常被報告之不良事件。

不良事件	事件數量	具有表徵/症狀之受試者數量	受試者 %
全身	**42**	**14**	**33.3%**
疼痛(合併計算)	31		
頭痛	4		
臉部水腫	3		
發燒	2		
消化系統	**16**	**10**	**27.8%**
噁心	12		
便秘	2		
嘔吐	2		
皮膚及其附屬器官	**10**	**7**	**19.4%**
皮膚搔癢	6		
皮疹	4		
呼吸系統	**4**	**2**	**5.6%**
呼吸疾病	4		
神經系統	**6**	**2**	**5.6%**
感覺異常	3		
焦慮	3		
造血及淋巴系統	**3**	**1**	**2.8%**
貧血	3		

一個肺栓塞的單一發生事件被報告可能考慮與產品有也許(possible)之關連性。這位受試者接受60 IU VWF:RCo/kg體重之劑量且FVIII:C值達到290%。

在外科手術或侵入性手術投予Alphanate (A-SD/HT)作為術中預防過度出血之療效及安全性評估之回溯性研究，39位受試者中有3位(7.7%)經歷6個藥物不良反應。4個被認為是輕度，2個被認為是中度。沒有受試者因不良反應而停止治療。這些藥物不良反應分別為皮膚搔癢，感覺異常 (2案例) 和出血 (全被認為是輕度)，以及一位受試者分別有中度的血球容積比(hematocrit)減少以及姿態性低血壓的情況。

在四位患有VWD孩童病患之前瞻性研究過程中，曾有一被報告之不良事件 (疼痛) 被認為與以經熱處理之Alphanate (A-SD/HT)治療有關連；在五位孩童受試者之回溯性臨床研究則無發生。

<上市後經驗>

下列不良反應已經在Alphanate (A-SD/HT)核准後被發現，因為這些反應是源自不確定族群的自願報告，無法可靠估計他們藥物使用頻率或者建立其引起的原因。

使用Alphanate (A-SD/HT)治療的病患中，曾有過敏／過敏性反應案例被報告(包括蕁麻疹、皮疹、皮膚搔癢、胸悶氣短、喘鳴聲、潮紅、心悸、噁心及嘔吐)。

下列是常被報告的不良反應：發燒、畏寒、頭痛、關節疼痛和疲勞。除此之外，一案例被報告發生腮腺腫脹、肺栓塞、股靜脈血栓、癲癇及短暫心肺休止。

[劑量及投予]

僅供靜脈注射使用。

抗血友病因子(AHF)之效價(FVIII:C活性)是以國際單位(IU)表示在產品標籤上。此外，Alphanate含有von Willebrand Factor: Ristocetin Cofactor (VWF:RCo)，以IU VWF:RCo/vial以表示供治療溫韋伯氏疾病(VWD)。

<A型血友病>

- Alphanate之治療應由具有治療血友病之醫師於其監督中開始使用。
- 劑量及治療時間須依據第八因子缺乏的嚴重程度、出血的位置及程度、抑制物的存在及病患的臨床狀況。於重度手術或生命威脅性出血狀況發生時，替代療法之小心控制特別重要。
- 給藥需求和給藥頻率是根據預期起始回應率2%的正常FVIII:C增加，以每IU FVIII:C/kg體重計算投予。

預期體內高峰增加之第八因子數值以IU/dL (或% normal)表示，可使用下列公式計算：

劑量(units) = 體重(kg) x 想要的FVIII增加量(IU/dL或% normal) x 0.5 (IU/kg per IU/dL)

或者

IU/dL (或% normal) = 總劑量(IU)/體重(kg) x 2

因此，若欲增加循環中第八因子數值至正常(100 IU/dL)的100%則需投予AHF劑量50 IU/kg。

投予劑量應依據病患之臨床反應來調整，包括個別需求、缺乏嚴重度、出血嚴重度、抑制物的存在及想要的第八因子增加量。病患對於Alphanate的藥物動力學(例如:半衰期、體內回收率)及臨床反應可能會不同。雖然劑量可以上述公式計算，仍高度建議若情況許可的話，應執行適當的實驗室檢驗包括系統性第八因子活性含量。**表六**中所顯示的是一般投予計量的指南。

表六：治療A型血友病之劑量指南

出血事件	劑量 (AHF FVIII:C IU/kg 體重)
輕度出血 • 大瘀青 • 明顯的割傷或撕裂傷 • 單純性關節出血	FVIII:C的數值應該要被提升到正常的30%(15 IU FVIII/kg，一天兩次)，直到出血停止和傷口癒合(1-2天)。
中度出血 • 鼻、口和牙齦出血 • 拔牙 • 血尿	FVIII:C的數值應該要被提升到正常的50%(25 IU FVIII/kg，一天兩次)，治療應該持續到傷口癒合(平均2-7天)。
嚴重出血 • 關節出血 • 肌肉出血 • 大創傷 • 血尿 • 顱內和腹腔內出血	FVIII:C的數值應該要被提升到正常的80-100%至少3-5天(40-50 IU FVIII/kg，一天兩次)，接著此治療之後FVIII數值應該維持在50%(25 IU FVIII/kg，一天兩次)，直到傷口癒合。嚴重出血可能需要治療長達10天。
手術	手術前，FVIII:C的數值應該要被提升到正常的80-100%(40-50 IU FVIII/kg)，接著7-10天或直到傷口癒合前，病人應該維持FVIII數值在60-100%(30-50 IU FVIII/kg，一天兩次)。

給藥需求和給藥頻率是根據預期起始回應率2%的FVIII:C增加，以每FVIII:C IU/kg體重計算(例如 2% per IU/kg)和平均FVIII:C的半衰期12小時。若是給藥研究已經確定某種特殊病人有較低的預期反應率，則應該隨之調整劑量。在適當計算的劑量下，若未能達到預期血漿中FVIII:C數值或者控制出血，可能表示發展出抑制物(一種FVIII:C的抗體)。若此情況出現應該記錄之，且抑制物的數值應該以適當的實驗室方法加以定量。發生這樣的情況下給予AHF必須個別化治療。

血漿第八因子的數值應該定期性地被監控以評估個別病患對劑量設計的反應。依據抑制物的數值及／或臨床反應，使用替代性繞道(bypass)治療製劑可能是適當的。

<溫韋伯氏疾病(VWD)>

- Alphanate之治療應由具有治療溫韋伯氏疾病(VWD)之醫師於其監督中開始使用。
- 每批Alphanate中VWF:RCo和Factor VIII的比率都不同，因此當所選擇批號改變時劑量必須重新評估。
- 劑量及治療時間須依據VWF缺乏的嚴重程度、出血的位置及程度及病患的臨床狀況。於重度手術或生命威脅性出血狀況發生時，替代療法之小心控制特別重要。應當避免FVIII數值超過150%之過量給藥。

中位數增加的VWF:RCo及FVIII:C體內再現率各為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)]，及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)]。

表七提供孩童和成年人患有溫韋伯氏疾病(VWD)之劑量指南。

表七：溫韋伯氏疾病手術和侵入性治療期間之預防劑量指南
(例外: 進行重度手術的Type 3病患)

輕度手術/出血		
	VWF:RCo	目標FVIII:C活性數值
手術前/程序前之劑量	成人：60 IU VWF:RCo/kg 體重 孩童：75 IU VWF:RCo/kg體重	40-50 IU/dL
維持之劑量	成人：40至60 IU VWF:RCo/kg體重，依臨床需求每8至12小時間隔一次，1至3天。 孩童：50至75 IU VWF:RCo/kg體重，依臨床需求每8至12小時間隔一次，1至3天。	40-50 IU/dL
安全性監測	至少每天監測一次peak及trough數值	至少每天監測一次peak及trough數值
治療目標(Trough)[a]	>50 IU/dL	>50 IU/dL
安全性參數[b]	應不超過150 IU/dL	應不超過150 IU/dL

重度手術/出血		
	VWF:RCo	目標FVIII:C 活性數值
手術前/程序前之劑量	成人：60 IU VWF:RCo/kg 體重 孩童：75 IU VWF:RCo/kg體重	100 IU/dL
維持之劑量	成人：40至60 IU VWF:RCo/kg 體重，依臨床需求每8至12小時間隔一次，至少3至7天。 孩童：50至75 IU VWF:RCo/kg 體重，依臨床需求每8至12小時間隔一次，至少3至7天。	100 IU/dL
安全性監測	至少每天監測一次peak及trough數值	至少每天監測一次peak及trough數值
治療目標(Trough)[a]	>50 IU/dL	>50 IU/dL
安全性參數[b]	應不超過150 IU/dL	應不超過150 IU/dL

[a] 治療目標引用自NHLBI Guidelines。
[b] 安全性參數摘錄自Mannucci 2009。

[使用及處理方法]【本藥限由醫師處方使用】

使用方法:

溶解後之Alphanate僅供靜脈注射使用。使用拋棄式塑膠注射器。溶解後不可再冷藏。溶解後之Alphanate於輸注投予前可儲放於室溫(不得超過 30°C)，但應在三個小時之內以靜脈輸注投予。將沒有用完的剩餘藥液丟棄於適當的安全容器內。Alphanate輸注投予速度不得超過10 mL/minute。若超過產品標籤所標示之有效期限，請勿使用。使用前請詳細核對標籤上之含量值(assay value)。進行稀釋及給藥時需使用無菌操作技術。剩餘之藥液禁止供後續使用，也不可儲存於冰箱。

藥物調配

應用無菌技術

1. 將稀釋液(無菌注射用水，USP)及濃縮劑(Alphanate)的溫度回升至少到室溫(但不得超過37°C)。
2. 將稀釋劑瓶頂端的塑膠瓶蓋移除。
3. 利用清潔藥劑例如酒精輕輕的將暴露在外的瓶塞表面擦拭乾淨。不要將多餘的清潔劑留駐瓶塞上。
4. 打開裝著Mix2Vial®的蓋子，將它保留於乾淨的外包裝內(圖1)。
5. 將稀釋劑小瓶垂直置於平坦表面並握緊，拿起尚留在外包裝內的Mix2Vial，安全的握住稀釋劑小瓶，垂直下壓Mix2Vial**藍色**終端，使套上稀釋劑的瓶蓋(圖2)。
6. 持續握住稀釋劑小瓶，小心的將Mix2Vial的乾淨外包裝移除，確保Mix2Vial仍附著於稀釋劑小瓶(圖3)。
7. 將產品主劑小瓶垂直置於平坦表面，並使已接上Mix2Vial的稀釋劑瓶倒立。
8. 安全地握穩產品主劑小瓶於平坦表面，**垂直下壓**Mix2Vial**清除(clear)**終端，使套上主劑小瓶的瓶蓋(圖4)，稀釋劑自動流入主劑小瓶內。(注意：若Mix2Vial連接在角落，將破壞主劑小瓶真空，而使稀釋劑無法流入主劑小瓶)。
9. 加入稀釋劑的主劑品仍連接著Mix2Vial，輕輕的打漩主劑品以使藥液完全溶解(圖5)，調配需時不過5分鐘，不可搖動瓶身。
10. 握住小瓶轉接器，逆時針旋轉，將Mix2Vial分成兩部份(圖6)，分開後將附帶Mix2Vial**藍色**終端的稀釋品丟棄。
11. 抽吸空氣進入空的無菌注射針筒，保持帶有Mix2Vial**清除(clear)**終端的主劑小瓶直立，壓及順時鐘方向旋轉將拋棄式針筒轉入Mix2Vial的螺旋鎖住部份，將空氣注入主劑小瓶內。
12. 鬆開針筒活塞，讓整體系統倒立，且慢慢抽拉針筒活塞，使藥液進入針筒(圖7)。
13. 當藥液完全流入針筒，穩穩的握住針筒大桶及空小瓶連接器處(保持針筒活塞面朝下)，從Mix2Vial拔出針筒(圖8)，垂直握住針筒並推壓活塞，直到沒有空氣留在針筒內，然後將針筒接到靜脈穿刺輸液套。
14. 注意：若同一病人需要輸注一瓶以上藥劑，在針筒連接到靜脈穿刺輸液套前，可經由個別未使用的Mix2Vial套子，將兩瓶藥液抽入同一針筒。
15. 調配好之藥液盡可能在三小時內使用。
16. 在溶液及容器情況允許下，供靜脈輸注藥品於調配後輸注前應肉眼檢查有無含顆粒性物質及變色。在嚴謹執行溶解程序後，偶爾仍會有一些小粒子殘留於溶液中。Mix2Vial可移除微粒而不會減少其標示的效價。
17. 使用後將所有輸注設備丟棄入適當安全的容器，不可重複使用。

圖 1　圖 2　圖 3　圖 4　圖 5　圖 6　圖 7　圖 8

[包裝]

Alphanate是以無菌、凍晶粉末的形式，裝在單一劑量的瓶中，並附有一瓶稀釋劑(無菌注射用水，USP)及一Mix2Vial過濾器輸液套。Factor VIII及VWF:RCo的活性則以國際單位標示於每瓶之外盒及標籤。

[貯存]

Alphanate於不超過25°C (77°F)下，可貯存三年。實際產品到期日須依外盒包裝所標示的EXP日期。稀釋液不可凍結。

[臨床研究]

VWD：非急需手術的預防-前瞻性研究

一項前瞻性，多中心之臨床研究，37位溫韋伯氏疾病(VWD)受試者(6位Type 1，16位Type 2A，3位Type 2 B，12位Type 3) 經歷59次外科手術，包括的20個牙科，7個骨科，8個胃腸科，6個胃腸科(診斷)，9個血管科，3個婦科，2個生殖泌尿科，2個皮膚科和2個頭頸科手術；為了要預防出血，投予Alphanate (A-SD)或Alphanate (A-SD/HT)(21位受試者給予Alphanate (A-SD)，18位受試者給予Alphanate (A-SD/HT)，2位受試者同時投予二種製劑) (請參閱**表八**)。在每項外科手術之前，研究員提供同性別且身材和年齡相似的正常人，經歷相同類型的外科手術期間，預期手術中血液損失的估計值。手術一小時前，起始輸注60 IU VWF:RCo/kg (若是病人小於18歲則輸注75 IU VWF:RCo/kg)。起始輸注15分鐘後取樣一次以決定血漿中FVIII:C的數值。為了使手術順利進行，此數值必須等於或者超過正常的100%。在這些外科手術中不可給予冷凍沉澱品(cryoprecipitate)或第八因子替代性產品。只有兩位受試者需輸注血小板。根據研究員的判斷於手術期間輸注A-SD和A-SD/HT，劑量60 IU VWF:RCo/kg (若是病人小於18歲則輸注75 IU VWF:RCo/kg)。

表八：外科手術的數量及類型

	治療		
外科手術類型	A-SD	A-SD/HT	Total
受試者數量	21	18	37^
牙科	14	6	20
皮膚科	1	1	2
胃腸科	4	4	8
胃腸科 (診斷)	6	0	6
生殖泌尿科	0	2	2
婦科	2	1	3
頭頸科	1	1	2
骨科	4	3	7
血管科	3	6	9
所有手術數量	35	24	59

^兩位病患同時接受兩種製劑: 因此受試者的總數不到欄位的總和。

手術後每8-12小時間隔輸注投予40到60 IU VWF:RCo/kg (50到75 IU VWF:RCo/kg對孩童病人)直到傷口開始癒合。在達到初期止血(primary hemostasis)之後，為了要維持第二期止血(secondary hemostasis)，在手術後第三天劑量要降低。請參見[劑量及投予]。

總括而言，55個輸注前出血時間延長(prolonged BT)的外科手術，投藥30分鐘後的出血時間(BT)完全校正改善的有18 (32.7%)位病人，部分校正改善的有24(43.6%)位病人，顯示為沒有校正改善的有12(21.8%)位病人，其中有一例並無研究(1.8%)。

平均的血液損失有比先前預期值低，出血超過預期值是與校正後的出血時間(BT)無關。有三位病患出血超過先前預期的50 mL。在後續受試者中，輸注後30分鐘內的出血時間(BT)，在其中一人是正常且只稍微地在兩個病人有延長的情況。

外科手術的輸注摘要數據歸入於**表九**。

表九：外科手術使用Alphanate (A-SD)和／或Alphanate (A-SD/HT)預防給藥

	A-SD	A-SD/HT	Total
病人數目	21	18	37*
外科手術數目	35	24	59
外科手術輸注的中位數(範圍)	3 (1-13)	4 (1-18)	4 (1-18)
中位劑量 IU VWF: RCo/kg			
輸注 #1 (範圍)	59.8 (19.8-75.1)	59.9 (40.6-75.0)	59.9 (19.8-75.1)
輸注 ≥ #2 總和 (範圍)	40.0 (4.5-75.1)	40.0 (10.0-63.1)	40.0 (4.5-75.1)

*兩位病患同時接受兩種製劑。

此外，依據研究過程之定義將手術分類為重度、輕度或侵入性手術，每項手術的結果為依據臨床評量分數表分類(極好、良好、差或者無)，並且如果結果是極好或良好則被認為是治療成功。這些結果顯示於**表十**。

表十：手術預防治療的效果 (研究員評估)：分析每治療事件Alphanate (A-SD/HT)

研究員結果評估	溫韋伯氏疾病(VWD)類型											
	Type 1 (4受試者，4個手術)			Type 2 (9受試者，13個手術)			Type 3 (5受試者，7個手術)			Total (18受試者，24個手術)		
	手術			手術			手術			手術		
	1	2	3	1	2	3	1	2	3	1	2	3
極好	1	0	2	5	1	5	5	0	1	11	1	8
良好	0	0	1	0	0	1	0	0	0	0	0	2
差	0	0	0	0	0	0	0	0	0	0	0	0
無	0	0	0	0	1	0	0	1	0	0	2	0

手術：1 = 輕度，2 = 重度，3 = 侵入性。
絕對頻率與成功結果的比例 = 22/24 (91.66%)。
成功預防受試者比例的95%信賴區間 (Confidence Interval, CI) = 0.7300到0.9897。

本次研究成果也被兩個具備相同領域與研究方法經驗的臨床審查委員獨立評估(每次手術類型和結果都根據臨床評量分數表)。

每位治療受試者中，手術預防治療的有效性結果(審查委員評估)總結於**表十一**。審查委員評估及分析後結果數據之間有高度一致性，只有一個成功數的減少(21/24與22/24)。

表十一：手術預防治療的效果 (審查委員評估)：分析每治療事件Alphanate (A-SD/HT)

	審查委員 1	審查委員 2
治療受試者數目	18	18
治療事件數目	24	24
成功數 絕對頻率和比例 (%)	22 (0.9166)	21 (0.8750)
*比例的95% 信賴區間	0.7300 to 0.9897	0.6763 to 0.9734

*精確預估成功預防受試者比例的95%信賴區間。

VWD：非急需手術的預防－回溯性研究

一項回溯性，多中心的研究評估Alphanate (A-SD/HT)用於溫韋伯氏疾病受試者，當給予DDAVP無效或不適當，但須進行手術或侵入性治療時當成預防過度失血的替代療法，研究評估在2004年9月和2005年12月之間進行的61項手術治療(39位受試者)。

在39位受試者中，18位是Type 1 VWD (46.2%)；12位是Type 2 VWD (30.8%)，並且9位是Type 3 VWD (23.1%)。全部受試者的中位數年齡是40歲；約一半的受試者是男性。

主要療效變數是每個外科手術或侵入性治療的整體治療結果，由研究員使用4分的文字評量分數表(4-point verbal rating score, VRS)評估：極好，良好，差，或者無(未註明有效性)。替代療法的結果分類是基於研究員臨床經驗並依據所提議的分數表進行。

次要療效變數是：

- 每日(第0日和第1日)每個外科手術或侵入性治療的結果，由研究員使用相同於主要療效力變數評估的4分VRS進行評分。第0日是手術日，而第1日是手術後的隔日。
- 每外科手術和侵入性治療的整體治療結果，由獨立裁判委員會以相同於主要療效變數4分的VRS評分。

此外，須召集一個獨立的審查委員會來評估療效結果，此委員會組成是由有過治療這些研究族群的相似醫學背景且具專門臨床技能的二位醫生組成，委員會須全然不知研究員的評分，並且每位委員獨立地不互相干擾評估結果。

超過90%的研究員和委員會的整體及每日評分結果都是有效的治療(“極好”或者“良好”)。主要療效分析結果在**表十二**。

表十二：研究員對手術整體評分為有效與非有效等級的比例 (n = 61)

Alphanate 治療結果	手術比例	95% 信賴區間	P 值[a]
有效[b]	95.1	87.8 - 98.6	< 0.0001
非有效[c]	4.9	1.4 - 12.2	

[a] 二項式試驗Binomial test H_0：<70%的手術治療的整體評分為有效)。
[b] 有效 = 研究員評分為“極好”或“良好”。
[c] 非有效 = 研究員評分為“差”或“無”。

研究員每日評分等級之分析結果在**表十三**。

表十三：研究員對手術每日評分為有效與非有效等級的比例 (n= 61)

研究日[a]	Alphanate 治療結果	手術比例	95% 信賴區間	P 值[b]
0	有效[c]	95.1	87.8 - 98.6	< 0.0001
	非有效[d]	4.9	1.4 - 12.2	
1	有效	91.8	83.5 - 96.7	< 0.0001
	非有效	8.2	3.3 - 16.5	

[a] 研究日0 = 手術當天。
[b] 二項式試驗Binomial test(H_0：<70%的手術治療的整體評分為有效)。
[c] 有效 = 研究員評分為“極好”或“良好”。
[d] 非有效 = 研究員評分為“差”或“無”。

委員整體評分等級之分析結果在**表十四**。

表十四：委員對手術整體評分為有效與非有效等級的比例 (n = 61)

Alphanate 治療結果	手術比例	95% 信賴區間	P 值[a]
有效[b]	91.8	83.5 - 96.7	< 0.0001
非有效[c]	8.2	3.3 - 16.5	

[a] 二項式試驗Binomial test (H_0：< 70%的手術治療的整體評分為有效)。
[b] 有效 = 委員評分為“極好”或“良好”。
[c] 非有效 = 委員評分為“差”或“無”。

研究員的整體評分依溫韋伯氏疾病(VWD)的類型摘要在**表十五**。

表十五：研究員依照溫韋伯氏疾病(VWD)類型對整體療效評分的數目(%)

研究員整體評分	溫韋伯氏疾病(VWD)類型							
	Type 1 (18位受試者，22個手術)		Type 2 (12位受試者，23個手術)		Type 3 (9位受試者，16個手術)		Total (39位受試者，61個手術)	
	重度	輕度[a]	重度	輕度	重度	輕度	重度	輕度
極好	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%)
良好	1 (14.3%)	3 (20.0%)	2 (50.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	3 (25.0%)	4 (8.2%)
差	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
無	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100%)	1 (6.7%)	1 (8.3%)	1 (2.0%)

[a] 輕度手術也包含侵入性手術。
[b] %為手術給予有效性評分之百分比。

大多數評分都是“極好”(每種溫韋伯氏疾病類型都≥ 81.3%)。九位Type 3受試者經歷1個重度及15個輕度手術。一位Type 3 VWD受試者的2個手術(1個重度及1個輕度)被給予整體療效評分為“無”，一位Type 2 VWD受試者的一個手術被給予整體療效評分為“差”。

整個回溯性研究之手術期間接受Alphanate的總劑量摘要在**表十六**。

表十六：依手術類型給予Alphanate (VWF: RCo)

	A-SD/HT
病人數目	39
外科手術數目	61
輸注平均數	5.9
每外科手術輸注中位數 (範圍)	3 (1-27)

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