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Alphanate®

Solvent Detergent / Heat Treated

ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)

3052361

DESCRIPTION

Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate® sterile, lyophilized concentrate of Factor VIII (AHF) and von Willebrand Factor (VWF), is intended for intravenous administration in the treatment of hemophilia A, acquired Factor VIII deficiency, 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) in International Units (IU) per vial. Each vial of Alphanate® also contains specific labeled amount of von Willebrand Factor Ristocetin Cofactor (VWF:RCo) activity expressed in IU. An IU is defined by the current international standard established by the World Health Organization. One IU of Factor VIII or one IU of VWF:RCo is approximately equal to the amount of Factor VIII or VWF:RCo 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 described in **Table 1.**

Table 1: Composition of Alphanate®

Active Ingredients: Factor VIII von Willebrand Factor	250 IU, 500 IU, 1000 IU, 1500 IU > 400 IU/1000 IU Factor VIII
Excipients:	Albumin Human, Arginine and Histidine

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. Since the number of virus particles inactivated by the process represents the maximum amount of virus added initially to the sample, these results indicate that all the virus added was killed to the assay limit of detection.[4]

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).[4] 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®.[4] It must be stated that no treatment method has yet been shown capable of totally eliminating all potential infectious virus in preparations of coagulation factor concentrates.

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

CLINICAL PHARMACOLOGY

Mechanism of Action

Antihemophilic Factor/von Willebrand Factor Complex (Human) (Factor VIII) and von Willebrand Factor (VWF) are constituents of normal plasma and are required for clotting. The administration of Alphanate® temporarily increases the plasma level of Factor VIII, thus minimizing the hazard of hemorrhage.[5,6] Factor VIII 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 Factor VIII.[7,8]

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 postinfusion.[4] 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.[4]

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® SD/HT (A-SD/HT) and an earlier formulation, Alphanate® SD (A-SD), which was treated with solvent-detergent but was not heat-treated.[9] Subjects received, in random order at least seven days apart, a single intravenous dose each of A-SD and A-SD/HT, 60 VWF:RCo IU/kg (75 VWF:RCo IU/kg in subjects younger than 18 years of age). Pharmacokinetic parameters were similar for the two preparations and indicated that they were biochemically equivalent. Pharmacokinetic analysis of A-SD/HT in the 14 subjects revealed the following results[9]: the median plasma levels of VWF:RCo rose from 0.17 IU/dL [mean, 0.2 ± 0.08 IU/dL; range: 0.1 to 0.5 IU/dL] at baseline to 3.43 IU/dL [mean, 3.5 ± 1.47 IU/dL; range: 1.5 to 5.9 IU/dL] 15 minutes post-infusion; median plasma levels of FVIII:C rose from 0.08 IU/dL [mean, 0.2 ± 0.34 IU/dL; range: 0.0 to 1.2 IU/dL] to 2.14 IU/dL [mean, 2.4 ± 0.72 IU/dL; range: 1.4 to 3.9 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 A-SD/HT, the median half-lives for VWF:RCo, FVIII:C and VWF:Ag were 6.91 hours (mean, 7.46 ± 3.20 hours, range, 3.68 to 16.22 hours), 20.87 hours (mean, 21.52 ± 7.21 hours; range: 7.19 to 32.20 hours), and 12.66 hours (mean, 13.03 ± 2.12 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: 1.3 to 5.7 (IU/dL)/(IU/kg)] for VWF:RCo and 1.94 (IU/dL)/(IU/kg) [mean, 2.14 ± 0.58 (IU/dL)/(IU/kg); range: 1.3 to 3.3 (IU/dL)/(IU/kg)] for FVIII:C.

Following infusion of both A-SD and 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.[9]

INDICATIONS AND USE

Hemophilia A or Acquired Factor VIII Deficiency

Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate®, is indicated for the prevention and control of bleeding in patients with Factor VIII deficiency due to hemophilia A or acquired Factor VIII deficiency.[10]

Von Willebrand Disease

Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate®, is also indicated for surgical and/or invasive procedure in patients with von Willebrand Disease (VWD), in whom desmopressin (DDAVP®) is either ineffective or contraindicated, except Type 3 patients undergoing major surgery.

CONTRAINDICATIONS

None known.

WARNINGS

Patients should be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur. It is recommended that the lot number of the vials used be recorded when Alphanate® is administered.

PRECAUTIONS

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.[11,12] Early reports might indicate a higher incidence in females. 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.

Infections

Because Antihemophilic Factor/von Willebrand Factor Complex (Human), 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. Despite these measures, such products can still potentially transmit disease; therefore, the risk of infectious agents cannot be totally eliminated. The physician should weigh the risks and benefits of the use of this product and should discuss these with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C.[13,14] Incubation in a solvent detergent mixture during the manufacturing process is designed to reduce the risk of transmitting viral infection.[13,14] However, medical opinion encourages hepatitis A and hepatitis B vaccinations for patients with hemophilia at birth or at the time of diagnosis.

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

Inhibitor Formation

Some patients develop inhibitors to Factor VIII. These inhibitors are circulating antibodies (i.e., globulins) that neutralize the procoagulant activity of Factor VIII. 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 antihemophilic factor preparations. 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.[15-17]

Reports in the literature suggest that patients with Type 3, severe von Willebrand Disease, may occasionally develop alloantibodies to von Willebrand factor after replacement therapy.[18] The risk of developing alloantibodies in patients with von Willebrand disease due to the use of this product is not known.

Information for Patients

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

Patients should be informed of a potential for viral infection such as parvovirus B19 or hepatitis A. Parvovirus B19 may most seriously affect seronegative pregnant women, or immunocompromised individuals. Patients should report any signs and symptoms of fever, sore throat, or joint soreness to the physician immediately.

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.

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. During a well controlled half-life and recovery clinical trial in patients previously treated with Factor VIII concentrates for Hemophilia A, the single pediatric patient receiving Alphanate® (solvent detergent non-heat treated) responded similarly when compared with 12 adult patients.[19] No adverse events were reported in either pediatric or adult patients with Alphanate®.

VWD Indication

Fifteen pediatric patients with von Willebrand Disease younger than 18 years of age were treated with non-heat (A-SD) and heat-treated (A-SD/HT) Alphanate® during the course of clinical studies.[4] In the retrospective study, five patients younger than 18 years of age were treated with heat-treated (A-SD/HT) Alphanate®.

ADVERSE REACTIONS

General

The most common adverse reactions may include urticaria, fever, chills, nausea, vomiting, headache, somnolence, or lethargy.

Occasionally, mild reactions occur following the administration of Antihemophilic Factor/von Willebrand Factor Complex (Human), such as allergic reactions, chills, nausea, or stinging at the infusion site.[19] If a reaction is experienced, and the patient requires additional Antihemophilic Factor/von Willebrand Factor Complex (Human), product from a different lot should be administered.

Massive doses of Antihemophilic Factor/von Willebrand Factor Complex (Human) have rarely resulted in acute hemolytic anemia, increased bleeding tendency or hyperfibrinogenemia.[20] 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.

Reports of thromboembolic events in VWD patients with other thrombotic risk factors receiving coagulation factor replacement therapy have been obtained from published literature. Early reports might indicate a higher incidence in females. Caution should be exercised and antithrombotic measures should be considered in all VWD patients in situations of high thrombotic risk.

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

Adverse Reactions in VWD Patients from Clinical Studies

In clinical studies of Alphanate® (A-SD/HT) in patients with VWD, adverse reactions occurred in 6 of 38 (15.8%) subjects and 17 of 299 (5.7%) infusions. The most common adverse events were pruritus, pharyngitis (throat tightness), paresthesia and headache, edema of the face, rash and chills. Except for one instance of pruritus, which was considered moderate in severity, all the adverse events were assessed as mild in severity.

A single incident of pulmonary embolus was reported that was considered to have a possible relationship to the product. This subject received the dose of 60 VWF:RCo IU/kg body weight and the FVIII:C level achieved was 290%.

In the retrospective study, 3 out of 39 subjects (7.7%) experienced 6 adverse drug reactions. Four were considered mild and 2 were considered moderate; and 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.

Only 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 subjects in the retrospective clinical study.[4]

Adverse Reaction Information from Spontaneous Reports

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.

These adverse reactions have been reported as swelling of the parotid gland, urticaria, nausea, shortness of breath, chest tightness, chills, fever, rigors, headache, flushing, vomiting, joint pain, seizure, pulmonary embolus, femoral venous thrombosis, itching and cardiorespiratory arrest.

DOSAGE AND ADMINISTRATION

Following reconstitution with the supplied diluent, Alphanate® should be administered intravenously within three hours after reconstitution to avoid the potential ill effect of any inadvertent bacterial contamination occurring during reconstitution. Alphanate® is administered by injection (plastic disposable syringes are recommended). Administer at room temperature, do not refrigerate after reconstitution, and discard any unused contents into the appropriate safety container.

Antihemophilic Factor (AHF) potency (Factor VIII:C activity) is expressed nominally in International Units (IU) on the product label. Additionally, each vial of Alphanate® also contains specific von Willebrand Factor:Ristocetin Cofactor (VWF:RCo) activity in IU for the treatment of VWD.

Hemophilia A

Dosing requirements and frequency of dosing is calculated on the basis of an expected initial response of 2% of normal FVIII:C increase per FVIII:C IU/kg body weight administered.[21,22] The *in vivo* increase in plasma Factor VIII can therefore be estimated by multiplying the dose of AHF per kilogram of body weight (FVIII:C IU/kg) by 2%. Thus, an administered AHF dose of 50 IU/kg will be expected to increase the circulating Factor VIII level by 100% of normal (100 IU/dL). The following formulas and examples illustrate these principles:

a) Expected plasma Factor VIII:C increase (% normal) = $\frac{\text{Number of FVIII:C IU administered} \times 2\%/\text{IU/kg}}{\text{body weight (kg)}}$

Example: A 70 kg adult administered AHF 2100 IU:

Plasma FVIII:C increase (% normal) = $\frac{2100 \text{ IU} \times 2\%/\text{IU/kg}}{70 \text{ kg}}$ = 60% normal plasma FVIII:C level

b) Dosage required (IU) = $\frac{\text{desired plasma Factor VIII increase (\% normal)} \times \text{body weight (kg)}}{2\%/\text{IU/kg}}$

Example: A 15 kg child with a baseline plasma FVIII level of 0%. To increase the plasma Factor VIII concentration to 100% of normal, the dosage required is as follows:

Dosage required (IU) = $\frac{100\%}{2\%/\text{IU/kg}} \times 15 \text{ kg} = 50 \text{ IU/kg} \times 15 \text{ kg} = 750 \text{ IU}$

The following dosages are presented as general guidance as shown in **Table 3**. It should be emphasized that the dosage of Alphanate® required for hemostasis must be individualized according to the needs of the patient, the severity of the deficiency, the severity of the hemorrhage, the presence of inhibitors, and the FVIII level desired. Adequacy of treatment must be judged by the clinical effects and situation and thus, the dosage may vary with individual cases.

Table 3: Dosage Guidelines for the Treatment of Hemophilia A

Hemorrhagic event	Dosage (AHF FVIII:C IU/kg Body Weight)
Minor hemorrhage: • Bruises • Cuts or scrapes • Uncomplicated joint hemorrhage	FVIII:C levels should be brought to 30% of normal (15 FVIII IU/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 FVIII IU/kg twice daily). Following this treatment period, FVIII levels should be maintained at 50% (25 FVIII IU/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 FVIII IU/kg). For the next 7-10 days, or until healing has been achieved, the patient should be maintained at 60-100% FVIII levels (25-50 FVIII IU/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.[23,25] 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.[15-17]

Plasma factor VIII levels should be monitored periodically to evaluate individual patient response to the dosage regime.

Von Willebrand Disease

Table 4 provides dosing guidelines for pediatric and adult patients with von Willebrand Disease.[24-26]

The amount of specific VWF:RCo and nominal Factor VIII contained in each vial of Alphanate® is indicated on the vial's label. The ratio of VWF:RCo to Factor VIII in Alphanate® varies by lot, so dosage should be re-evaluated whenever lot selection is changed.

Table 4: Dosage Guidelines for the Prophylaxis During Surgery and Invasive Procedure of von Willebrand Disease (Except Type 3 Subjects Undergoing Major Surgery)

Bleeding Prophylaxis for Surgical or Invasive Procedures	Dosage (AHF VWF:RCo IU/kg Body Weight)
Adult	Pre-operative dosage: 60 VWF:RCo IU/kg body weight. Subsequent infusions: 40 to 60 VWF:RCo IU/kg body weight at 8 to 12 hour intervals as clinically needed. Dosing may be reduced after the third postoperative day. Continue treatment until healing is complete.
	Minor procedure: VWF activity of 40%-50% during 1 to 3 days postoperative.
	Major procedure: VWF activity of 40%-50% during at least 3 to 7 days postoperative.
Pediatric	Initial dosage: 75 VWF:RCo IU/kg body weight. Subsequent infusions: 50 to 75 VWF:RCo IU/kg body weight at 8 to 12 hour intervals as clinically needed. Dosing may be reduced after the third postoperative day. Continue treatment until healing is complete.

INSTRUCTIONS FOR USE AND HANDLING

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.

Solution preparation:

1. Warm the vial and syringe but not above 30 °C.
2. Attach the plastic plunger to the syringe containing diluent.
3. Remove the filter from its packaging. Remove the grey rubber cap from the syringe tip and then attach the syringe to the filter.
4. Remove the vial adaptor from its packaging. Attach the vial adaptor to the syringe-filter assembly.
5. Remove the plastic flip-top cap from the concentrate vial and wipe the exposed rubber with the antiseptic wipe provided.
6. Place the syringe/filter/adaptor assembly over the top of the concentrate vial and pierce the stopper with the adaptor needle.
7. Transfer all the Water for Injections into the concentrate vial by depressing the syringe plunger.
8. Gently swirl the vial until all the concentrate has dissolved. As with other parenteral solutions, do not use the solution if it is not properly dissolved or particles are visible.
9. Briefly separate the syringe/filter and vial/adaptor assemblies to release any vacuum.
10. Invert the concentrate vial and draw up the solution through the filter into the syringe.
11. Prepare the injection site, separate the filter/vial adaptor from the syringe. Inject the solution intravenously using the butterfly needle provided or a sterile needle.

Administer slowly at a rate not exceeding 10 ml/minute. Rapid administration of a Factor VIII concentrate may result in vasomotor reactions.

After reconstitution with the Water for Injections solvent provided, the product should be used immediately.

Do not re-use the administration sets.

Any unused product or waste material should be disposed of in accordance with local requirements.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Alphanate® is supplied in sterile, lyophilized form in single dose vials accompanied by a suitable volume of diluent (sterile water for injections), according to AHF potency.

Alphanate® is packaged with a prefilled syringe with diluent (sterile water for injections) and accessories for injection.

STORAGE

Alphanate® is stable for three years, up to the expiration date printed on its label, provided that the storage temperature does not exceed 30 °C. Do not freeze diluent.

CLINICAL STUDIES

Prophylaxis for Elective Surgery

Thirty seven 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 administering A-SD or A-SD/HT (21 subjects were administered A-SD and 16 were administered A-SD/HT, 2 received both products) for bleeding prophylaxis (see **Table 5**). 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 VWF:RCo IU/kg (75 VWF:RCo IU/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 VWF:RCo IU/kg (75 VWF:RCo IU/kg for patients less than 18 years of age) was administered according to the judgment of the investigator.

Table 5: 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 VWF:RCo IU/kg (50 to 75 VWF:RCo IU/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.

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 6.**

Table 6: Prophylaxis with A-SD and/or 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 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 7.**

Table 7: Effect of Treatment on Surgical Prophylaxis (Investigator Evaluation): Analysis per Treated Event (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 8**. 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 8: Effect of Treatment on Surgical Prophylaxis (Referee Evaluation): Analysis per Treated Event (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.

A retrospective 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.

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." 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 9.**

Table 9: 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_1: < 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 10.**

Table 10: 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_1: < 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 11.**

Table 11: 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_1: < 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 12.**

Table 12: 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%)	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.

The majority of ratings were "excellent" (≥ 81.3% in each VWD type). Only 2 procedures 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 13.**

Table 13: 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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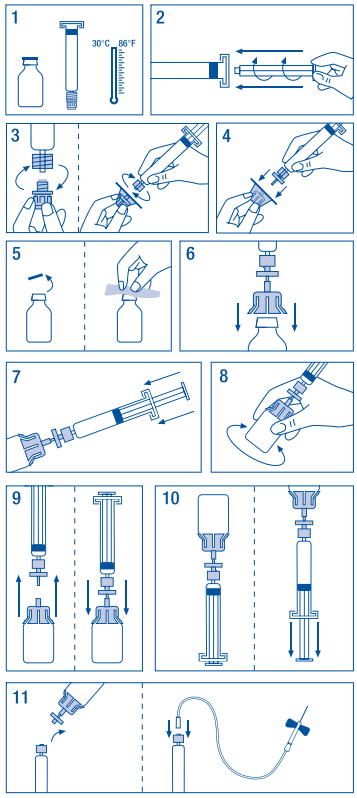

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