Alphanate® (Antihemophilic Factor/von Willebrand Factor Complex [Human])

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

ALPHANATE (antihemophilic factor/von Willebrand factor complex [human])
Lyophilized Powder for Solution for Intravenous Injection
Initial U.S. Approval: 1978

INDICATIONS AND USAGE
ALPHANATE, (antihemophilic factor/von Willebrand factor complex [human]), is indicated for:

- Control and prevention of bleeding in adult and pediatric patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe WVD (Type 3) undergoing major surgery.

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

Dose (2.1)
Treatment and Prevention of Bleeding Episodes and Excess Bleeding During and After Surgery in Patients with Hemophilia A
- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Dosing frequency determined by the type of bleeding episode and the recommendation of the treating physician.

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

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

CONTRAINDICATIONS
Do not use 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 are possible. Discontinue treatment with ALPHANATE and administer appropriate emergency treatment should symptoms of anaphylaxis or severe hypersensitivity occur (5.1).
- Development of activity-neutralizing antibodies may occur in patients receiving FVIII containing products (5.2).
- Thromboembolic events (TE) may occur in WVD patients, especially with known risk factors. Monitor patients for signs and symptoms of TE (5.3).
- Intravascular hemolysis may occur with infusion of large doses of Antihemophilic Factor/von Willebrand Factor Complex. Should this condition occur and lead to progressive hematologic anemia, discontinue administration of ALPHANATE and consider alternative therapy (5.4).
- Rapid administration may result in vasomotor reactions (5.5).
- ALPHANATE is made from human plasma and may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.6).
- Perform assays to determine if FVIII inhibitors are present (5.7).

ADVERSE REACTIONS
The most frequent adverse drug reactions reported with ALPHANATE in >1% of infusions were pruritus, headache, back pain, paresthesia, respiratory distress, facial edema, pain, rash and chills (6).
To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

See 17 for PATIENT COUNSELING INFORMATION
Revised: March 2017

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

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

2.1 Dose
Treatment and Prevention of Bleeding Episodes and Excess Bleeding During and After Surgery in Patients with Hemophilia A
- Dose 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. The expected in vivo peak increase in FVIII level expressed as IU/dL (or % of normal) can be estimated using the following formulas:

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

or

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

- Titrate dose and frequency to the patient’s clinical response, including individualized needs, severity of the deficiency, severity of the hemorrhage, presence of inhibitors, and FVIII level desired. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to ALPHANATE.
- Table 1 provides dosage guidelines for the control and prevention of bleeding episodes in hemophilia A patients. Dosing should aim at maintaining a plasma factor VIII activity level at or above the plasma levels (in IU/dL or in % of normal) outlined in the table.
Table 1: Dosage Guidelines for Patients with Hemophilia A

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>Factor VIII: C Level Required (% of normal)</th>
<th>Doses (IU/kg)</th>
<th>Frequency of Doses (hours)</th>
<th>Duration of Therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>30</td>
<td>15</td>
<td>12 (twice daily)</td>
<td>Until hemorrhage stops and healing has been achieved (1–2 days).</td>
</tr>
<tr>
<td>Moderate</td>
<td>50</td>
<td>25</td>
<td>12 (twice daily)</td>
<td>Until healing has been achieved (2–7 days, on average).</td>
</tr>
<tr>
<td>Major</td>
<td>80–100</td>
<td>Initial: 40–50</td>
<td>Maintenance: 25</td>
<td>For at least 3–5 days.</td>
</tr>
<tr>
<td>Surgery</td>
<td>Prior to surgery: 80–100</td>
<td>40–50</td>
<td>Once</td>
<td>For the next 7–10 days, or until healing has been achieved.</td>
</tr>
<tr>
<td></td>
<td>After surgery: 60–100</td>
<td>30–50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Treatment and Prevention of Excess Bleeding During and After Surgery or Other Invasive Procedures in Patients with von Willebrand Disease

- The ratio of VWF:RCo to FVIII in ALPHANATE varies by lot, so with each new lot, check IU VWF:RCo/vial to ensure accurate dosing.
- Dosage and duration of treatment depend on the severity of the VWF deficiency, the location and extent of bleeding, and the patient’s clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- The median incremental in vivo recoveries of VWF:RCo and FVIII:C were 3.12 (IU/dL)/(IU/kg) (mean, 3.29 ± 1.46 (IU/dL)/(IU/kg); range: 1.28 to 5.73 (IU/dL)/(IU/kg)) for VWF:RCo and 1.95 (IU/dL)/(IU/kg) (mean, 2.13 ± 0.58 (IU/dL)/(IU/kg); range: 1.33 to 3.32 (IU/dL)/(IU/kg)) for FVIII:C.
- Table 2 provides dosing guidelines for pediatric and adult patients with von Willebrand Disease.3 4

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VWF:RCo</th>
<th>Target FVIII:C Activity Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>40–50 IU/dL</td>
<td></td>
</tr>
<tr>
<td>Therapeutic Goal (Trough):&gt;50 IU/dL</td>
<td>&gt;50 IU/dL</td>
<td></td>
</tr>
<tr>
<td>Safety Monitoring: Peak and trough at least once daily</td>
<td>Peak and trough at least once daily</td>
<td></td>
</tr>
<tr>
<td>Safety Parameter: Should not exceed 150 IU/dL</td>
<td>Should not exceed 150 IU/dL</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 continued

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VWF:RCo</th>
<th>Target FVIII:C Activity Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative/pre-procedure dose: Adults: 60 IU VWF:RCo/kg body weight. Pediatrics: 75 IU VWF:RCo/kg body weight.</td>
<td>100 IU/dL</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>100 IU/dL</td>
<td></td>
</tr>
<tr>
<td>Therapeutic Goal (Trough):&gt;50 IU/dL</td>
<td>&gt;50 IU/dL</td>
<td></td>
</tr>
<tr>
<td>Safety Monitoring: Peak and trough at least daily</td>
<td>Peak and trough at least daily</td>
<td></td>
</tr>
<tr>
<td>Safety Parameter: Should not exceed 150 IU/dL</td>
<td>Should not exceed 150 IU/dL</td>
<td></td>
</tr>
</tbody>
</table>

a The therapeutic goal is referenced in the NHLBI Guidelines.7
b The safety parameter is extracted from Mannucci 2009.8

2.2 Reconstitution
1. Always use aseptic technique.
2. Ensure that concentrate (ALPHANATE) and diluent (Sterile Water for Injection, USP) are at room temperature (but not above 37 °C) before reconstitution.
3. Remove the plastic flip off cap from the diluent vial.
4. Gently swab the exposed stopper surface with a cleansing agent such as alcohol trying to avoid leaving any excess cleansing agent on the stopper.
5. Open the Mix2Vial package by peeling away the lid (Figure 1). Leave the Mix2Vial in 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. Place the diluent vial upright on an even surface and hold the vial tight and pick up the Mix2Vial in its clear outer packaging. Holding the diluent vial securely, push the blue end of the Mix2Vial vertically down through the diluent vial stopper (Figure 2).
7. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial set, ensuring the Mix2Vial remains attached to the diluent vial (Figure 3).
8. Place the product vial upright on an even surface, invert the diluent vial with the Mix2Vial attached.
9. While holding the product vial securely on a flat surface, push the clear end of the Mix2Vial set vertically down through the product vial stopper (Figure 4). The diluent will automatically transfer out of its vial into the product vial.
10. With the diluent and product vials still attached to the Mix2Vial, gently swirl the product vial to ensure the product is fully dissolved (Figure 5). Reconstitution requires less than 5 minutes. Do not shake the vial.
11. Disconnect the Mix2Vial into two separate pieces (Figure 6) by holding each vial adapter and twisting counterclockwise. After separating, discard the diluent vial with the blue end of the Mix2Vial.
12. Draw air into an empty, sterile syringe. Keeping the product vial upright with the clear end of the Mix2Vial attached, screw the disposable syringe onto the luer lock portion of the Mix2Vial device by pressing and twisting clockwise. Inject air into the product vial.

13. While keeping the syringe plunger depressed, invert the system upside down and draw the reconstituted product into the syringe by pulling the plunger back slowly (Figure 7).

14. When the reconstituted product has been transferred into the syringe, firmly hold the barrel of the syringe and the clear vial adapter (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial (Figure 8). Hold the syringe upright and push the plunger until no air is left in the syringe. Attach the syringe to a venipuncture set. NOTE: If the same patient is to receive more than one vial of concentrate, the contents of two vials may be drawn into the same syringe through a separate unused Mix2Vial set before attaching to the venipuncture set.

15. When reconstitution procedure is strictly followed, a few small particles may occasionally remain. The Mix2Vial set will remove particles and the labeled potency will not be reduced.

16. Discard all reconstitution equipment after use into the appropriate safety container. Do not reuse.

17. Use the prepared drug as soon as possible within 3 hours after reconstitution.

2.3 Administration

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

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

5.2 Neutralizing Antibodies

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

5.3 Thromboembolic Events

Thromboembolic events have been reported in von Willebrand Disease patients receiving replacement therapy with Antifibrinolytic Factor/von Willebrand Factor Complexes, especially in those with known risk factors for thrombosis including but not limited to elderly age, previous thrombosis, metabolic syndrome, cancer, surgery, oral contraceptive and hormone therapy, diabetes, hypertension, hyperlipidemia, smoking, and pregnancy.1 Monitor plasma levels of WFC activity and FVIII activities to avoid sustained excessive VWF and FVIII activity levels (greater than 150 IU/dL), which may increase the risk of thrombotic events, during continued treatment of replacement therapy with Antifibrinolytic Factor/von Willebrand Factor Complexes. Consider antithrombotic measures in VWD patients at risk for thrombosis [see Adverse Reactions (6)].

5.4 Intravascular Hemolysis

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

5.5 Vasomotor Reactions

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

5.6 Transmissible Infectious Agents

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

5.7 Monitoring Laboratory Tests

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

Monitor plasma levels of WFC and FVIII activities to avoid sustained excessive WFC and FVIII activity levels (greater than 150 IU/dL), which may increase the risk of thrombotic events, particularly in patients with known risk factors.

6 ADVERSE REACTIONS

Serious adverse drug reactions (ADRs) observed in patients receiving ALPHANATE include anaphylaxis/hypersensitivity reactions. Thromboembolic events also have been observed in patients receiving ALPHANATE for WVD [see Warnings and Precautions (5)].

6.1 Clinical Trial Experience

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

Hemophilia A

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

von Willebrand Disease

In the prospective clinical study of ALPHANATE (using both ALPHANATE Solvent Detergent (A-SD, a previous generation product) and ALPHANATE Solvent Detergent/Heat Treated (A-SD/HT, the current generation product)) in subjects with von Willebrand Disease, ADRs occurred in 5 of 36 subjects (13.9%) treated with ALPHANATE.

Sixty-one total ADRs were reported in 204 infusions. The majority of ADRs were rated as mild (55 of 61 [90.2%]). Six ADRs (9.8%) were rated as moderate. No reactions rated as serious were reported. The adverse drug reaction grading scale is defined as follows:
- Mild: the event was noted but the administration of the compound was not interrupted; the event resolved spontaneously or no treatment was required beyond administration of nonprescription analgesics.
- Moderate: the administration of the compound was not necessarily interrupted; the event required momentary treatment with prescription drugs and produced no sequelae.

Overall, the proportion of infusions associated with ADRs was 14 of 204 infusions (6.9%). The most common ADRs reported (> 1% of infusions) were pruritus, headache, back pain, dyspepsia, respiratory distress, facial edema, pain, rash, and chills. One incident of pulmonary embolism was reported that was considered to have a possible relationship to the product. This subject received a dose of 60 IU WFC/RCo/kg body weight and the FVIII:C level achieved was 290%.
In the retrospective study conducted to determine the efficacy and safety of ALPHANATE (A-SD/HT) in a surgical or invasive procedure setting as perioperative prophylaxis against excessive bleeding, [see Clinical Studies (14)], 3 out of 39 subjects (7.7%) experienced 6 adverse drug reactions. Four were considered mild and 2 were considered moderate. No subject discontinued their treatment due to an adverse drug reaction. The adverse drug reactions were pruritus, parasthesia (2 events) and hemorrhage (all considered mild), and one event each of moderate hematocrit decrease and orthostatic hypotension.

One adverse drug reaction (pain) related to the treatment with heat-treated ALPHANATE (A-SD/HT) was reported in the four pediatric subjects with von Willebrand Disease during the course of the prospective study and in none of the five pediatric subjects in the retrospective clinical study.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Hemophilia A

A total of 21 children (ages 7-16) were included in clinical trials with ALPHANATE. Subjects received ALPHANATE weekly for prophylaxis or suspected bleeds. They were successfully treated for 1499 bleeding episodes or as prophylaxis to prevent them (e.g. pain in the joint). The median number of units needed to treat the bleeds was 420 IU, with a range of 210 to 1620 IU. Adult and pediatric subjects did not differ in their response to treatment.

Von Willebrand Disease

The hemostatic efficacy of ALPHANATE has been studied in 20 pediatric subjects (ages 7-18) with VWD. Based on the data from a subset of these subjects, age had no effect on the number of units needed to treat the bleeds was 420 IU, with a range of 210 to 1620 IU. Adult and pediatric subjects did not differ in their response to treatment.

8.5 Geriatric Use

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

11 DESCRIPTION

ALPHANATE, (anithemophilic factor/von Willebrand factor complex [human]), is a sterile, lyophilized concentrate of FVIII (AHF) and von Willebrand Factor (VWF).

ALPHANATE is prepared from pooled human plasma by cryoprecipitation of FVIII, fractional solubilization, and further purification employing heparin-coupled, cross-linked agarose which has an affinity to the heparin binding domain of FVIII/von Willebrand Complex. The product is treated with a mixture of tri-n-butyl phosphate (TNBP) and polysorbate 80 to inactivate enveloped viruses. The product is also subjected to an 80 °C heat treatment step for 72 hours to inactivate enveloped viruses, such as Human Immunodeficiency viruses (HIV), as well as marker viruses such as Sindbis virus (SIN, a model for Hepatitis C virus), Vesicular Stomatitis virus (VSV, a model for large, enveloped RNA virus), Bovine Herpes virus (BHV, a model for Hepatitis B virus) and Bovine Viral Diarrhea virus (BVD, a model for Hepatitis C virus). In vitro inactivation studies to evaluate the dry heat treatment (80 °C, 72 hours) step in the manufacture of ALPHANATE were conducted to assess the capability of the step to inactivate enveloped viruses, such as Human Immunodeficiency viruses (HIV), as well as marker viruses such as Sindbis virus (SIN, a model for Hepatitis C virus), Vesicular Stomatitis virus (VSV, a model for large, enveloped RNA virus), Bovine Herpes virus (BHV, a model for Hepatitis B virus) and Bovine Viral Diarrhea virus (BVD, a model for Hepatitis C virus). In vitro inactivation studies to evaluate the dry heat treatment (80 °C, 72 hours) step in the manufacture of ALPHANATE were conducted to assess the capability of the step to inactivate both enveloped and non-enveloped viruses, such as Hepatitis A virus (HAV), human Poliovirus Sabin type 2 (POL, a model for HAV), Canine Parvovirus (CPV, a model for Parvovirus B19), BHV and BVD. Other steps in the manufacturing process of ALPHANATE (precipitation with 3.5% polyethylene glycol (PEG), heparin affinity chromatography and hifololization) were also evaluated for virus elimination capability using several enveloped and non-enveloped viruses as shown in Table 3.

Table 3: Virus Log Reduction

<table>
<thead>
<tr>
<th>Virus (Model Virus for)</th>
<th>3.5% PEG Precipitation</th>
<th>Solvent–Detergent</th>
<th>Column Chromatography</th>
<th>Lyophilization</th>
<th>Dry Heat Cycle (80°C, 72 h)</th>
<th>Total Log Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHV (HBV)</td>
<td>&lt; 1.0</td>
<td>3.7</td>
<td>0.8</td>
<td>2.7</td>
<td>2.1</td>
<td>≥ 2.9</td>
</tr>
<tr>
<td>BVD (HCV)</td>
<td>&lt; 1.0</td>
<td>4.1</td>
<td>0.2</td>
<td>3.9</td>
<td>4.9</td>
<td>≥ 9.7</td>
</tr>
<tr>
<td>POL (HAV)</td>
<td>3.3</td>
<td>0.7</td>
<td>4.4</td>
<td>0.5</td>
<td>2.5</td>
<td>≥ 9.7</td>
</tr>
<tr>
<td>CPV (B19)</td>
<td>1.2</td>
<td>–</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
<td>4.1</td>
<td>5.3</td>
</tr>
<tr>
<td>VSV</td>
<td>–</td>
<td>4.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>≥ 4.1</td>
</tr>
<tr>
<td>SIN (HCV)</td>
<td>≥ 4.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>≥ 4.7</td>
</tr>
<tr>
<td>HIV-1</td>
<td>&lt; 1.0</td>
<td>≥ 11.1</td>
<td>≥ 2.0</td>
<td>–</td>
<td>–</td>
<td>≥ 13.1</td>
</tr>
<tr>
<td>HIV-2</td>
<td>≥ 6.1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>≥ 6.1</td>
</tr>
<tr>
<td>HAV</td>
<td>–</td>
<td>–</td>
<td>2.1</td>
<td>–</td>
<td>–</td>
<td>≥ 5.8</td>
</tr>
</tbody>
</table>

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 log10), affinity chromatography (3.50 log10) and saline precipitation (1.36 log10). These studies provide reasonable assurance that low levels of CJD/CJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

A pharmacokinetic study was conducted in 12 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 dosages of each product, 60 IU FVIII:C-US/dl plasma per IU FVIII infused/kg body weight.

Pharmacokinetics in von Willebrand Disease (VWD)

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

The pharmacokinetic data in VWD are summarized in Table 4.

Table 4: Pharmacokinetic data in VWD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma VWF:RCo (Mean ± SD)</th>
<th>Plasma FVIII:C (Mean ± SD)</th>
<th>Plasma VWF:Ag (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Mean plasma levels (IU/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.86 ± 4.97</td>
<td>21.00 ± 33.83</td>
<td>-</td>
</tr>
<tr>
<td>15 minutes post infusion</td>
<td>215.50 ± 101.70</td>
<td>215.29 ± 94.26</td>
<td>-</td>
</tr>
<tr>
<td>T½ (Half-life in hours)</td>
<td>7.67 ± 3.32</td>
<td>21.58 ± 7.95</td>
<td>13.06 ± 2.20</td>
</tr>
</tbody>
</table>

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 reduced after the third post-operative day. For additional surgical procedures using ALPHANATE SD/HT only were categorized as major, minor or invasive procedures according to definitions used in the study. The outcome of each surgery was evaluated according to a clinical rating scale (excellent, good, poor or none) and was considered successful if the outcome was excellent or good. Study results also were evaluated independently by two referees with clinical experience in this field in the same way (subject categorization and outcome of each surgery according to a clinical rating scale). There was a high level of agreement between the referee evaluations and the analyzed outcome data, with a decrease of only a single success in achieving hemostasis (21/24 [referees evaluation] vs. 22/24 [investigators evaluation]).

A retrospective, multi-center study was performed to assess the efficacy of ALPHANATE (A-SD/HT) as replacement therapy in preventing excessive bleeding in subjects with congenital VWD undergoing surgical or invasive procedures, for whom DDAVP was ineffective or inadequate. A total of 61 surgeries/procedures in 39 subjects were evaluated. The majority of ratings were considered “excellent” (≥ 81.3% in each VWD type). Nine Type 3 subjects underwent 1 major and 15 minor procedures. Two procedures (1 major and 1 minor) in 1 subject with Type 3 VWD received an overall efficacy rating of “poor,” and one minor procedure in a subject with Type 2 VWD received an overall efficacy rating of “poor.”

In addition, an independent referee committee was convened to evaluate the efficacy outcomes. More than 90% of the surgical outcomes received an investigator and referee’s overall and daily rating of “effective” (“excellent” or “good”) in achieving hemostasis/preventing bleeding. The majority of ratings were considered “excellent” (≥ 81.3% in each VWD type). Nine Type 3 subjects underwent 1 major and 15 minor procedures. Two procedures (1 major and 1 minor) in 1 subject with Type 3 VWD received an overall efficacy rating of “none,” and one minor procedure in a subject with Type 2 VWD received an overall efficacy rating of “poor.”

15 REFERENCES


16 **HOW SUPPLIED/STORAGE AND HANDLING**

**How Supplied**

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

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

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

**Storage and Handling**

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

17 **PATIENT COUNSELING INFORMATION**

Advised the patient:

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