ALPHANATE- antihemophilic factor/von willebrand factor complex (human)
GRIFOLS USA, LLC

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: (1)

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

DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only.
ALPHANATE contains the labeled amount of factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial (2).
Dose (2.1)
Treatment and Prevention of Bleeding Episodes and Excess Bleeding During and After Surgery in Patients with Hemophilia A

- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Dosing frequency determined by the type of bleeding episode and the recommendation of the treating physician.

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

- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals LLC at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 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: 11/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

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

2 DOSAGE AND ADMINISTRATION

For intravenous injection after reconstitution only

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

2.1 Dose

Treatment and Prevention of Bleeding Episodes and Excess Bleeding During and After Surgery in Patients with Hemophilia A

- Dosage and duration of treatment depend on the severity of the FVIII deficiency, the location and extent of bleeding, presence of inhibitors, and the patient's clinical condition. Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes.
- Dosing requirements and frequency of dosing is calculated on the basis of an expected initial response of 2% of normal FVIII:C increase per IU FVIII:C/kg body weight administered.[1] The expected *in vivo* peak increase in FVIII level expressed as IU/dL (or % of normal) can be estimated using the following formulas:

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

or

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

- Titrate dose and frequency to the patient's clinical response, including individualized needs, severity of the deficiency, severity of the hemorrhage, presence of inhibitors, and FVIII level desired. Patients may vary in their pharmacokinetic (e.g., half-life, *in vivo* recovery) and clinical responses to ALPHANATE.
- Table 1 provides dosage guidelines for the control and prevention of bleeding

episodes in hemophilia A patients. Dosing should aim at maintaining a plasma factor VIII activity level at or above the plasma levels (in IU/dL or in % of normal) outlined in the table.

Table 1: Dosage Guidelines for Patients with Hemophilia A

Type of Bleeding	FVIII:C Level Required(% of normal)	Doses(IU/kg)	Frequency of Doses(hours)	Duration of Therapy (days)
Minor • Large bruises • Significant cuts or scrapes • Uncomplicated joint hemorrhage	30	15	12 (twice daily)	Until hemorrhage stops and healing has been achieved (1–2 days).
Moderate • Nose, mouth and gum bleeds • Dental extractions Hematuria	50	25	12 (twice daily)	Until healing has been achieved (2–7 days, on average).
Major • Joint hemorrhage • Muscle hemorrhage • Major trauma • Hematuria • Intracranial and intraperitoneal bleeding	80–100	Initial: 40–50 Maintenance: 25	12 (twice daily)	For at least 3–5 days Until healing has been achieved for up to 10 days. Intracranial hemorrhage may require prophylaxis therapy for up to 6 months.
Surgery	Prior to surgery: 80–100 After surgery: 60–100	40–50 30–50	Once 12 (twice daily)	Prior to surgery For the next 7–10 days, or until healing has been achieved.

- Monitoring parameters:
  - Monitor plasma FVIII levels periodically to evaluate individual patient response to the dosage regimen.
  - If dosing studies have determined that a particular patient exhibits a lower/higher

than expected response and shorter/longer half-life, adjust the dose and the frequency of dosing accordingly.
    - Failure to achieve the expected plasma FVIII:C level or to control bleeding after an appropriately calculated dosage may be indicative of the development of an inhibitor (an antibody to FVIII:C). Quantitate the inhibitor level by appropriate laboratory procedures and document its presence. Treatment with AHF in such cases must be individualized.[2]

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

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

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

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

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

[a] The therapeutic goal is referenced in the NHLBI Guidelines.[7]

[b] The safety parameter is extracted from Mannucci 2009.[8]

2.2 Reconstitution

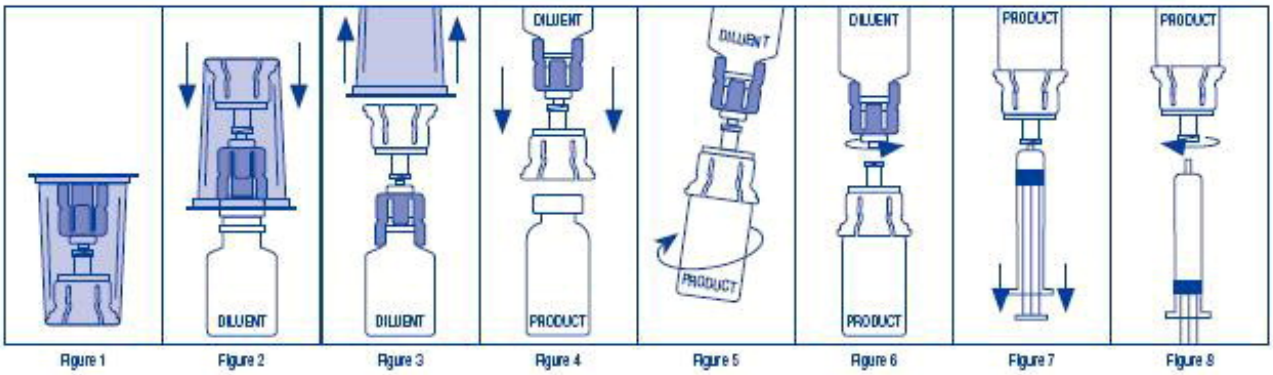
1. Always use aseptic technique.
2. Ensure that concentrate (ALPHANATE) and diluent (Sterile Water for Injection, USP) are at room temperature (but not above 37 ˚C) before reconstitution.
3. Remove the plastic flip off cap from the diluent vial.
4. Gently swab the exposed stopper surface with a cleansing 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 the clear outer packaging.
6. Place the diluent vial upright on an even surface and hold the vial tight and pick up the Mix2Vial in its clear outer packaging. Holding the diluent vial securely, push the **blue** end of the Mix2Vial vertically down through the diluent vial stopper (Figure 2).
7. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial set, ensuring the Mix2Vial remains attached to the diluent vial (Figure 3).
8. Place the product vial upright on an even surface, invert the diluent vial with the Mix2Vial attached.
9. While holding the product vial securely on a flat surface, push the **clear** end of the Mix2Vial set **vertically** down through the product vial stopper (Figure 4). The diluent will automatically transfer out of its vial into the product vial.

   NOTE: If the Mix2Vial is connected at an angle, the vacuum may be released from the product vial and the diluent will not transfer into the product vial.
10. With the diluent and product vials still attached to the Mix2Vial, gently swirl the product vial to ensure the product is fully dissolved (Figure 5). Reconstitution

requires less than 5 minutes. Do not shake the vial.

11. Disconnect the Mix2Vial into two separate pieces (Figure 6) by holding each vial adapter and twisting counterclockwise. After separating, discard the diluent vial with the **blue** end of the Mix2Vial.
12. Draw air into an empty, sterile syringe. Keeping the product vial upright with the **clear** end of the Mix2Vial attached, screw the disposable syringe onto the luer lock portion of the Mix2Vial device by pressing and twisting clockwise. Inject air into the product vial.
13. While keeping the syringe plunger depressed, invert the system upside down and draw the reconstituted product into the syringe by pulling the plunger back slowly (Figure 7).
14. When the reconstituted product has been transferred into the syringe, firmly hold the barrel of the syringe and the **clear** vial adapter (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial (Figure 8). Hold the syringe upright and push the plunger until no air is left in the syringe. Attach the syringe to a venipuncture set.

    NOTE: If the same patient is to receive more than one vial of concentrate, the contents of two vials may be drawn into the same syringe through a separate unused Mix2Vial set before attaching to the venipuncture set.
15. When reconstitution procedure is strictly followed, a few small particles may occasionally remain. The Mix2Vial set will remove particles and the labeled potency will not be reduced.
16. Discard all reconstitution equipment after use into the appropriate safety container. Do not reuse.
17. Use the prepared drug as soon as possible within 3 hours after reconstitution.



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, hypotension, rash, nausea, vomiting, paresthesia, restlessness, wheezing and dyspnea. Discontinue use of ALPHANATE if hypersensitivity symptoms occur, and initiate appropriate treatment.

5.2 Neutralizing Antibodies

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

5.3 Thromboembolic Events

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

therapy with Antihemophilic Factor/von Willebrand Factor Complexes. Consider antithrombotic measures in VWD patients at risk for thrombosis [see *Adverse Reactions (6)*].

5.4 Intravascular Hemolysis

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

5.5 Vasomotor Reactions

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

5.6 Transmissible Infectious Agents

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

5.7 Monitoring Laboratory Tests

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

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

6 ADVERSE REACTIONS

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

6.1 Clinical Trial Experience

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

Hemophilia A

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

von Willebrand Disease

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

Sixty-one total ADRs were reported in 204 infusions. The majority of ADRs were rated as mild (55 of 61 [90.2%]). Six ADRs (9.8%) were rated as moderate. No reactions rated as serious were reported. The adverse drug reaction grading scale is defined as follows:

- Mild: the event was noted but the administration of the compound was not interrupted; the event resolved spontaneously or no treatment was required beyond administration of nonprescription analgesics.
- Moderate: the administration of the compound was not necessarily interrupted; the event required momentary treatment with prescription drugs and produced no sequelae.

Overall, the proportion of infusions associated with ADRs was 14 of 204 infusions (6.9%).

The most common ADRs reported (> 1% of infusions) were pruritus, headache, backpain, paresthesia, respiratory distress, facial edema, pain, rash, and chills.

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

In the retrospective study conducted to determine the efficacy and safety of ALPHANATE (A-SD/HT) in a surgical or invasive procedure setting as perioperative prophylaxis against excessive bleeding, [see *Clinical Studies (14)*], 3 out of 39 subjects (7.7%) experienced 6 adverse drug reactions. Four were considered mild and 2 were considered moderate. No subject discontinued their treatment due to an adverse drug reaction. The adverse drug reactions were pruritus, paresthesia (2 events) and hemorrhage (all considered mild), and one event each of moderate hematocrit decrease and orthostatic hypotension.

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

6.2 Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship

to drug exposure.

The most common post-marketing ADRs reported include allergic/hypersensitivity reactions, nausea, fever, joint pain, fatigue, and infusion site pain.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Hemophilia A

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

Von Willebrand Disease

The hemostatic efficacy of ALPHANATE has been studied in 20 pediatric subjects (ages 7-18) with VWD. Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo. Adult and pediatric subjects did not differ in their response to treatment.

8.5 Geriatric Use

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

11 DESCRIPTION

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

ALPHANATE is prepared from pooled human plasma by cryoprecipitation of FVIII, fractional solubilization, and further purification employing heparin-coupled, cross-linked agarose which has an affinity to the heparin binding domain of VWF/FVIII:C complex. The product is treated with a mixture of tri-n-butyl phosphate (TNBP) and polysorbate

80 to inactivate enveloped viruses. The product is also subjected to an 80 °C heat treatment step for 72 hours to inactivate enveloped and non-enveloped viruses. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products.

ALPHANATE is labeled with the antihemophilic factor potency (FVIII:C activity) in International Units (IU) FVIII/vial and with VWF:RCo activity expressed in IU VWF:RCo/vial. The activities are referenced to their respective international standards established by the World Health Organization. One IU of FVIII or one IU of VWF:RCo is approximately equal to the amount of FVIII or VWF:RCo activity in 1 mL of freshly-pooled human plasma.

ALPHANATE contains human albumin as a stabilizer, resulting in a final container concentrate with a specific activity of at least 5 FVIII:C IU/mg total protein. ALPHANATE contains no preservatives.

The composition of ALPHANATE after reconstitution is as follows:

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

Viral Reduction Capacity

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

In vitro inactivation studies to evaluate the solvent detergent treatment (0.3% Tri-n-butyl Phosphate and 1.0% Polysorbate 80) step in the manufacture of ALPHANATE were conducted to assess the capability of the step to inactivate enveloped viruses, such as Human Immunodeficiency viruses (HIV), as well as marker viruses such as Sindbis virus (SIN, a model for Hepatitis C virus), Vesicular Stomatitis virus (VSV, a model for large, enveloped RNA virus), Bovine Herpes virus (BHV, a model for Hepatitis B virus) and Bovine Viral Diarrhea virus (BVD, a model for Hepatitis C virus). *In vitro* inactivation studies to evaluate the dry heat treatment (80 °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 lyophilization) were also evaluated for virus elimination capability using several enveloped and non-enveloped viruses as shown in **Table 3**.

Table 3: Virus Log Reduction

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.3 Pharmacokinetics

Pharmacokinetics in Hemophilia A

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

Pharmacokinetics in von Willebrand Disease (VWD)

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

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

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

Table 4: Pharmacokinetic data in VWD

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

Following infusion of both ALPHANATE (A-SD) and ALPHANATE (A-SD/HT), an increase in

the size of VWF multimers was seen and persisted for at least 24 hours. The shortening of the BT was transient, lasting less than 6 hours following treatment and did not correlate with the presence of large and intermediate size VWF multimers.[14]

14 CLINICAL STUDIES

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

Table 5: Number of and Types of Surgical Procedures

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

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

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

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

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

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

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

* Two subjects received both products

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

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

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

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

The primary efficacy variable was the overall treatment outcome for each surgical or invasive procedure, as rated by the investigator using a 4-point verbal rating scale (VRS): “excellent,” “good,” “poor,” or “none (no indication of efficacy).” The categorization of the replacement treatment outcome was based upon the investigator’s

clinical experience and defined in **Table 7**.

Table 7: Rating Scale and Clinical Efficacy of ALPHANATE Therapy

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

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

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

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

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

Potency	NDC	Assay Color Code
250 IU FVIII/5 mL single dose vial	68516-4611-1 or 68516-4616-1	250 IU FVIII Range – gray box
500 IU FVIII/5 mL single dose vial	68516-4612-1 or 68516-4617-1	500 IU FVIII Range - green box

1000 IU FVIII/10 mL single dose vial	68516-4613-2 or 68516-4618-2	1000 IU FVIII Range – blue box
1500 IU FVIII/10 mL single dose vial	68516-4614-2 or 68516-4619-2	1500 IU FVIII Range – orange box
2000 IU FVIII/10 mL single dose vial	68516-4615-2 or 68516-4620-2	2000 IU FVIII Range - magenta box

Storage and Handling

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

17 PATIENT COUNSELING INFORMATION

Advise the patient:

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

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

3063713

Principal Display Panel – 250 IU Vial Label

NDC 68516-4605-1 **250 IU FVIII Range**

Antihemophilic Factor/
von Willebrand Factor
Complex (Human)
Alphanate® 5 mL

Solvent Detergent / Heat Treated

Storage: Store at temperatures
not exceeding 25 °C (77 °F).

Rx only. Single dose container for intravenous administration only.

GRIFOLS U.S. License No. 1694

Instructions: Reconstitute with 5 mL of Sterile Water for Injection, USP. Administer promptly after reconstitution and do not refrigerate. Discard unused contents. For information on dosage and directions for administration, see accompanying pamphlet. Contains no preservatives. The patient and physician should discuss the risks and benefits of this product.

Grifols Biologicals LLC
5555 Valley Boulevard
Los Angeles, CA 90032, U.S.A.

Lot

EXP

IU FVIII/Vial

IU VWF:RCo/Vial 3063712

Lot

IU FVIII/Vial

IU VWF:RCo/Vial

Alphanate® 5 mL NDC 68516-4605-1

Principal Display Panel – 250 IU Carton Label

NDC 68516-4616-1 **250 IU FVIII Range**

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

Solvent Detergent / Heat Treated

Rx only
For Intravenous Administration 5 mL

GRIFOLS

Contents: One vial Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate®, one vial 5 mL Sterile Water for Injection, USP, one Mix2Vial® filter transfer set, and directions for use.

Composition:
Factor VIII, von Willebrand Factor, Arginine, Albumin and Histidine.
Contains no preservatives.
Administer within three hours of reconstitution.
Discard unused content.

GRIFOLS

Warning:
This product is prepared from large pools of human plasma. Human blood and its components may transmit infectious agents. See package insert, WARNINGS AND PRECAUTIONS.

Instructions: The patient and physician should discuss the risks and benefits of this product. For information on dosage and directions for administration, see enclosed package insert.

Storage: Store at temperatures not exceeding 25 °C (77 °F). Do not freeze.
Single dose container for intravenous administration only.

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GRIFOLS

3063711

GTIN 00368516461617
LOT XXXXXXXXXX
EXP DDMMMYYYY
SN XXXXXXXXXX XXXXXX
IU FVIII/Vial XXXX
IU VWF: RCo/Vial XXXX

Principal Display Panel – 500 IU Vial Label

NDC 68516-4606-1 **500 IU FVIII Range**

Antihemophilic Factor/
von Willebrand Factor
Complex (Human)
Alphanate® 5 mL

Solvent Detergent / Heat Treated
Storage: Store at temperatures not exceeding 25 °C (77 °F).
Rx only. Single dose container for intravenous administration only.

GRIFOLS U.S. License No. 1694

Instructions: Reconstitute with 5 mL of Sterile Water for Injection, USP. Administer promptly after reconstitution and do not refrigerate. Discard unused contents. For information

on dosage and directions for administration, see accompanying pamphlet. Contains no preservatives. The patient and physician should discuss the risks and benefits of this product.

Grifols Biologicals LLC
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Los Angeles, CA 90032, U.S.A.

Lot

EXP

IU FVIII/Vial

IU VWF:RCo/Vial 3063710

Lot

IU FVIII/Vial

IU VWF:RCo/Vial

Alphanate® 5 mL NDC 68516-4606-1

Principal Display Panel – 500 IU Carton Label

NDC 68516-4617-1 **500 IU FVIII Range**

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

Solvent Detergent / Heat Treated

Rx only
For Intravenous Administration 5 mL

GRIFOLS

Contents:
One vial Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate®, one vial 5 mL Sterile Water for Injection, USP, one Mix2Vial® filter transfer set, and directions for use.

Composition:
Factor VIII, von Willebrand Factor, Arginine, Albumin and Histidine.
Contains no preservatives.
Administer within three hours of reconstitution.
Discard unused contents.

GRIFOLS

Warning:
This product is prepared from large pools of human plasma. Human blood and its components may transmit infectious agents. See package insert, WARNINGS AND PRECAUTIONS.

Instructions: The patient and physician should discuss the risks and benefits of this product. For information on dosage and directions for administration, see enclosed package insert.

Storage: Store at temperatures not exceeding 25 °C (77 °F). Do not freeze.
Single dose container for intravenous administration only.

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U.S. License No. 1694

GRIFOLS

3063709

GTIN 00368516461716
LOT XXXXXXXXXX

EXP DDMMMYYYY
SN XXXXXXXXXX XXXXXX
IU FVIII/Vial XXXX
IU VWF: RCo/Vial XXXX

Principal Display Panel – 1000 IU Vial Label

NDC 68516-4607-2 **1000 IU FVIII Range**

Antihemophilic Factor/
von Willebrand Factor
Complex (Human)
Alphanate® **10 mL**

Solvent Detergent / Heat Treated
Storage: Store at temperatures
not exceeding 25 °C (77 °F).
Rx only. Single dose container for
intravenous administration only.

GRIFOLS U.S. License No. 1694

Instructions: Reconstitute
with 10 mL of Sterile Water
for Injection, USP. Administer

promptly after reconstitution and do not refrigerate. Discard unused contents. For information on dosage and directions for administration, see accompanying pamphlet. Contains no preservatives. The patient and physician should discuss the risks and benefits of this product.

Grifols Biologicals LLC
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Los Angeles, CA 90032, U.S.A.

Lot

EXP

IU FVIII/Vial

IU VWF:RCo/Vial 3063708

Lot

IU FVIII/Vial

IU VWF:RCo/Vial

Alphanate® **10 mL** NDC 68516-4607-2

Principal Display Panel – 1000 IU Carton Label

NDC 68516-4618-2 **1000 IU FVIII Range**

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

Solvent Detergent / Heat Treated

Rx only
For Intravenous Administration 10 mL

GRIFOLS

Contents:
One vial Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate®, one vial 10 mL Sterile Water for Injection, USP, one Mix2Vial® filter transfer set, and directions for use.

Composition:
Factor VIII, von Willebrand Factor, Arginine, Albumin and Histidine.
Contains no preservatives.
Administer within three hours of reconstitution.
Discard unused contents.

GRIFOLS

Warning:
This product is prepared from large pools of human plasma. Human blood and its components may transmit infectious agents. See package insert, WARNINGS AND PRECAUTIONS.

Instructions: The patient and physician should discuss the risks and benefits of this product. For information on dosage and directions for administration, see enclosed package insert.

Storage: Store at temperatures not exceeding 25 °C (77 °F). Do not freeze.
Single dose container for intravenous administration only.

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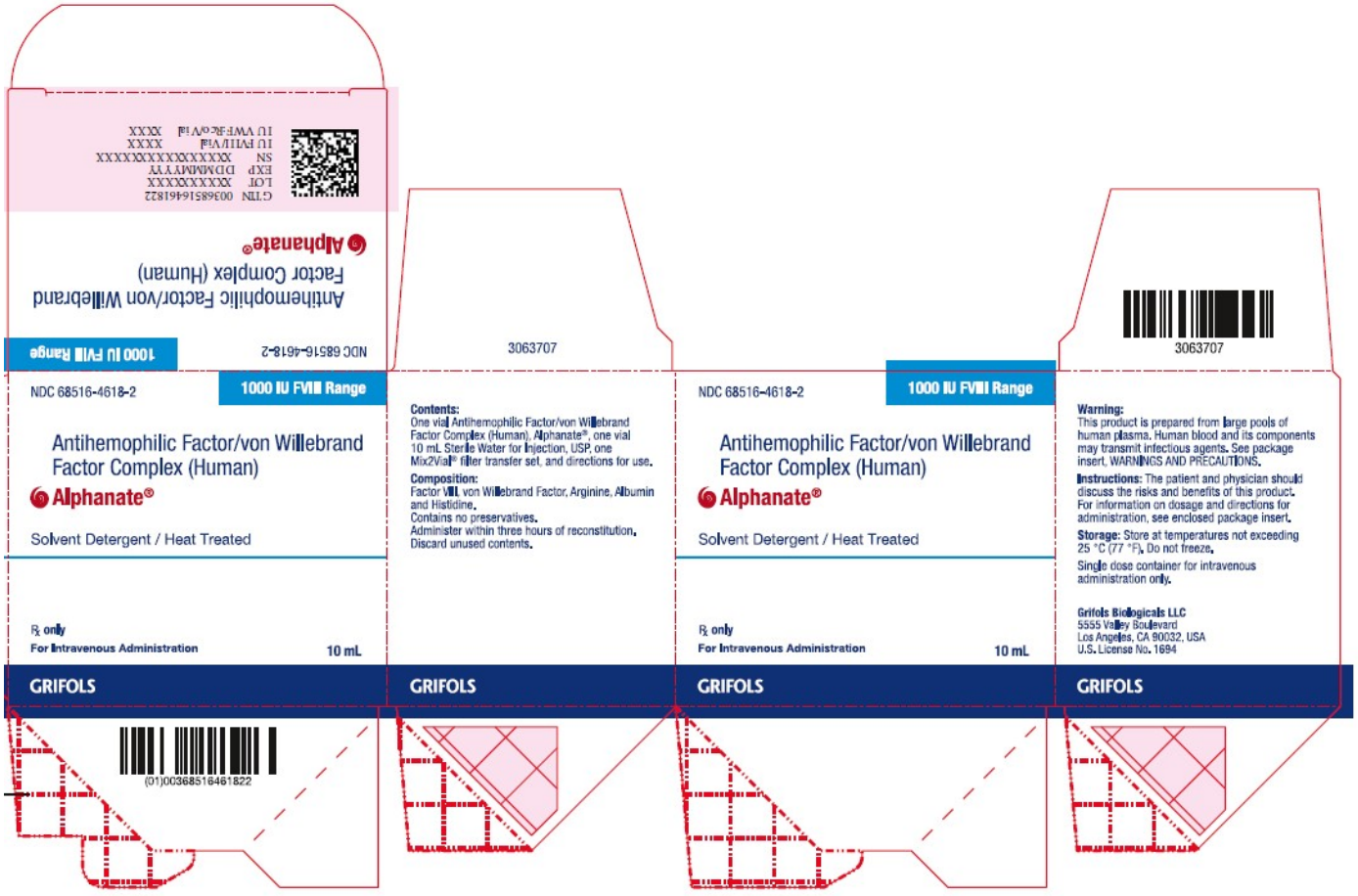
GRIFOLS

3063707

GTIN 00368516461822
LOT XXXXXXXXXX
EXP DDMMMYYYY
SN XXXXXXXXXX XXXXXX
IU FVIII/Vial XXXX
IU VWF: RCo/Vial XXXX



Principal Display Panel – 1500 IU Vial Label

NDC 68516-4608-2 **1500 IU FVIII Range**

Antihemophilic Factor/
von Willebrand Factor
Complex (Human)
Alphanate® 10 mL

Solvent Detergent / Heat Treated
Storage: Store at temperatures not exceeding 25 °C (77 °F).
Rx only. Single dose container for intravenous administration only.

GRIFOLS U.S. License No. 1694

Instructions: Reconstitute with 10 mL of Sterile Water for Injection, USP. Administer promptly after reconstitution and do not refrigerate. Discard unused contents. For information on dosage and directions for administration, see accompanying pamphlet. Contains no preservatives. The patient and physician should discuss the risks and benefits of this product.

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Los Angeles, CA 90032, U.S.A.

Lot

EXP

IU FVIII/Vial

IU VWF:RCo/Vial 3063706

Lot

IU FVIII/Vial

IU VWF:RCo/Vial

Alphanate®10 mL NDC 68516-4608-2

Principal Display Panel – 1500 IU Carton Label

NDC 68516-4619-2 **1500 IU FVIII Range**

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

Solvent Detergent / Heat Treated

Rx only
For Intravenous Administration 10 mL

GRIFOLS

Contents:
One vial Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate®, one vial 10 mL Sterile Water for Injection, USP, one Mix2Vial® filter transfer set, and directions for use.

Composition:
Factor VIII, von Willebrand Factor, Arginine, Albumin and Histidine.
Contains no preservatives.
Administer within three hours of reconstitution.
Discard unused contents.

GRIFOLS

Warning:
This product is prepared from large pools of human plasma. Human blood and its components may transmit infectious agents. See package insert, WARNINGS AND PRECAUTIONS.

Instructions: The patient and physician should discuss the risks and benefits of this product. For information on dosage and directions for administration, see enclosed package insert.

Storage: Store at temperatures not exceeding 25 °C (77 °F). Do not freeze.
Single dose container for intravenous administration only.

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U.S. License No. 1694

GRIFOLS

3063705

GTIN 00368516461921
LOT XXXXXXXXXX
EXP DDMMMYYYY
SN XXXXXXXXXX XXXXXX
IU FVIII/Vial XXXX
IU VWF: RCo/Vial XXXX

Principal Display Panel – 2000 IU Vial Label

NDC 68516-4610-2 **2000 IU FVIII Range**

Antihemophilic Factor/
von Willebrand Factor
Complex (Human)
Alphanate® 10 mL

Solvent Detergent / Heat Treated
Storage: Store at temperatures
not exceeding 25 °C (77 °F).

Rx only. Single dose container for intravenous administration only.

GRIFOLS U.S. License No. 1694

Instructions: Reconstitute with 10 mL of Sterile Water for Injection, USP. Administer promptly after reconstitution and do not refrigerate. Discard unused contents. For information on dosage and directions for administration, see accompanying pamphlet. Contains no preservatives. The patient and physician should discuss the risks and benefits of this product.

Grifols Biologicals LLC
5555 Valley Boulevard
Los Angeles, CA 90032, U.S.A.

Lot

EXP

IU FVIII/Vial

IU VWF:RCo/Vial 3063704

Lot
10
IU FVIII/Vial

IU VWF:RCo/Vial

Alphanate®10 mL NDC 68516-4608-2

Principal Display Panel – 2000 IU Carton Label

NDC 68516-4620-2 **2000 IU FVIII Range**

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

Solvent Detergent / Heat Treated

Rx only
For Intravenous Administration 10 mL

GRIFOLS

Contents:
One vial Antihemophilic Factor/von Willebrand Factor Complex (Human), Alphanate®, one vial 10 mL Sterile Water for Injection, USP, one Mix2Vial® filter transfer set, and directions for use.

Composition:
Factor VIII, von Willebrand Factor, Arginine, Albumin and Histidine.
Contains no preservatives.
Administer within three hours of reconstitution.
Discard unused contents.

GRIFOLS

Warning:
This product is prepared from large pools of human plasma. Human blood and its components may transmit infectious agents. See package insert, WARNINGS AND PRECAUTIONS.

Instructions: The patient and physician should discuss the risks and benefits of this product. For information on dosage and directions for administration, see enclosed package insert.

Storage: Store at temperatures not exceeding 25 °C (77 °F). Do not freeze.
Single dose container for intravenous administration only.

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Los Angeles, CA 90032, USA
U.S. License No. 1694

GRIFOLS

3063703

GTIN 00368516462027
LOT XXXXXXXXXX
EXP DDMMMYYYY
SN XXXXXXXXXX XXXXXX
IU FVIII/Vial XXXX
IU VWF: RCo/Vial XXXX

Principal Display Panel – 5 mL Vial Label

NDC 76297-002-02

Sterile Water for Injection, USP

5 mL

Rx only

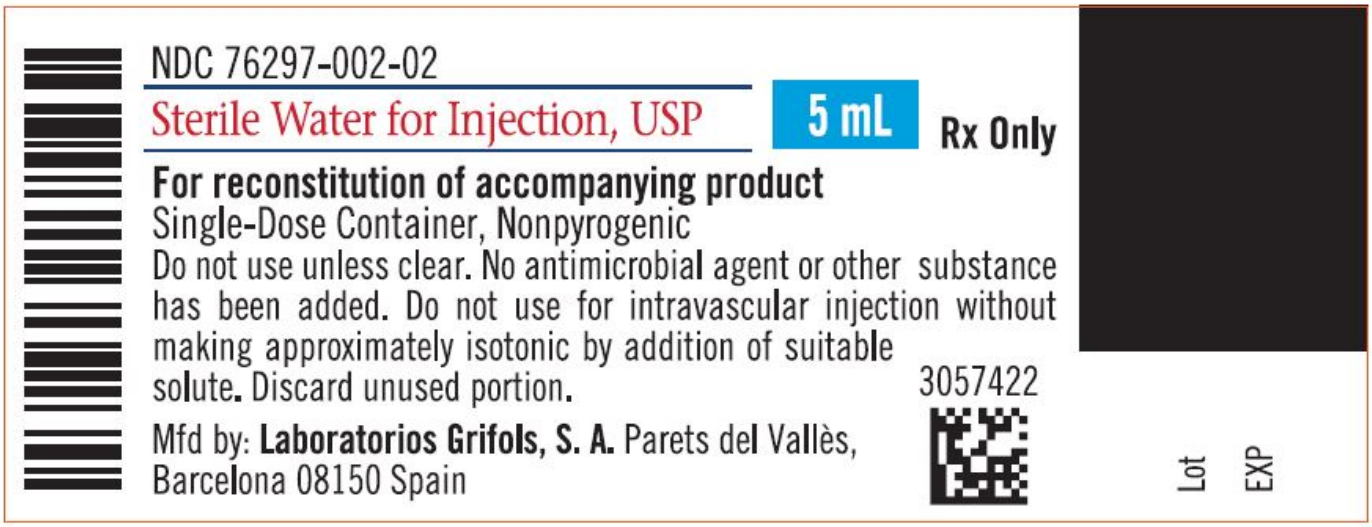
3057422

For reconstitution of accompanying product
Single-Dose Container, Nonpyrogenic
Do not use unless clear. No antimicrobial agent or other substance has been added. Do not use for intravascular injection without making approximately isotonic by addition of suitable solute. Discard unused portion.

Mfd by: **Laboratorios Grifols, S.A.** Parets del Vallès,
Barcelona 08150 Spain

Lot

EXP



Principal Display Panel – 10 mL Vial Label

NDC 76297-002-12

Sterile Water for Injection, USP

10 mL

Rx only

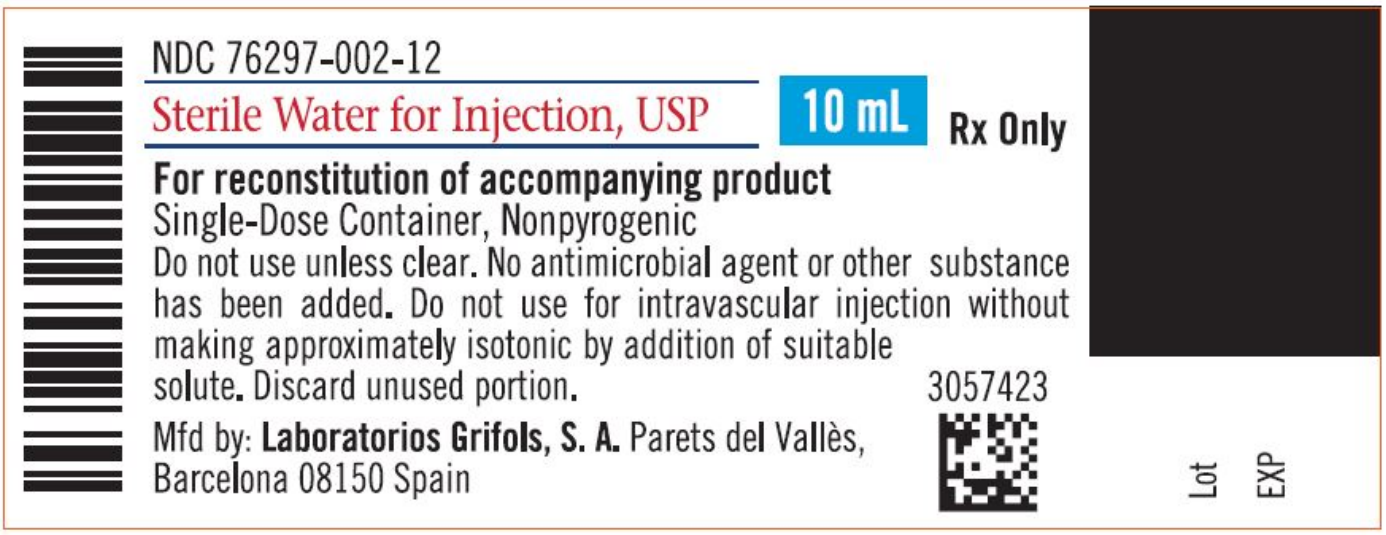
3057423

For reconstitution of accompanying product
Single-Dose Container, Nonpyrogenic
Do not use unless clear. No antimicrobial agent or other substance has been added. Do not use for intravascular injection without making approximately isotonic by addition of suitable solute. Discard unused portion.

Mfd by: **Laboratorios Grifols, S.A.** Parets del Vallès,
Barcelona 08150 Spain

Lot

EXP



Principal Display Panel – 5 mL Vial Label

NDC 68516-1001-1

Sterile Water for Injection, USP

5 mL
Rx only

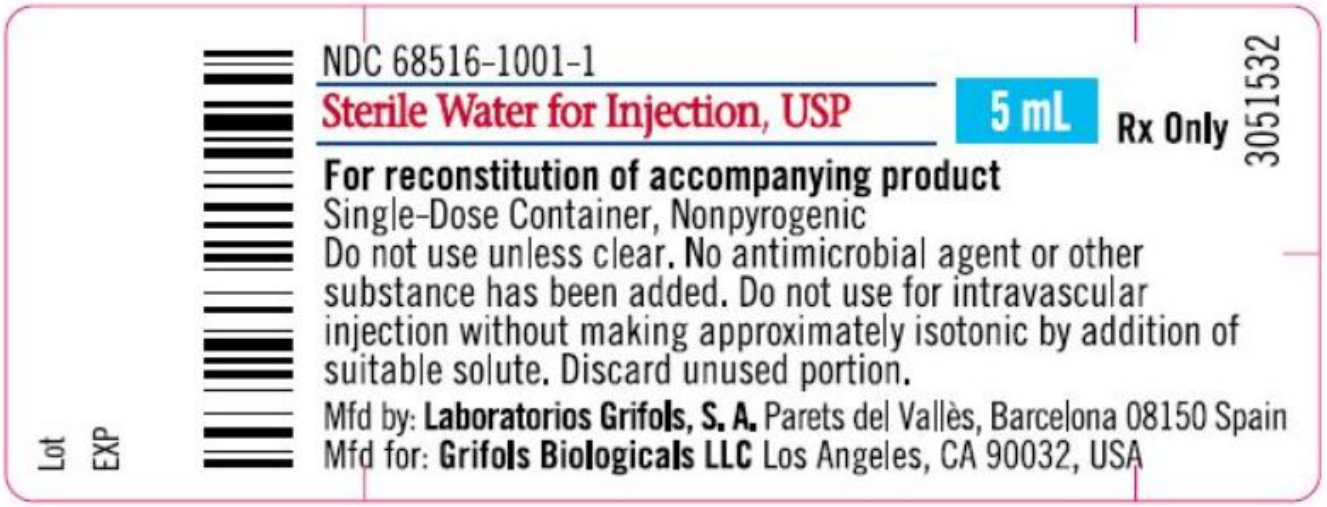
3051532

For reconstitution of accompanying product
Single-Dose Container, Nonpyrogenic
Do not use unless clear. No antimicrobial agent or other substance has been added. Do not use for intravascular injection without making approximately isotonic by addition of suitable solute. Discard unused portion.

Mfd by: **Laboratorios Grifols, S.A.** Parets del Vallès, Barcelona 08150 Spain
Mfd for: Grifols Biologicals LLC Los Angeles, CA 90032, USA

Lot

EXP



Principal Display Panel – 10 mL Vial Label

NDC 68516-1002-2

Sterile Water for Injection, USP

10 mL
Rx only

3051533

For reconstitution of accompanying product
Single-Dose Container, Nonpyrogenic
Do not use unless clear. No antimicrobial agent or other substance has been added. Do not use for intravascular injection without making approximately isotonic by addition of suitable solute. Discard unused portion.

Mfd by: **Laboratorios Grifols, S.A.** Parets del Vallès, Barcelona 08150 Spain
Mfd for: Grifols Biologicals LLC Los Angeles, CA 90032, USA

Lot

EXP

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4611

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4611-1	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL	5 mL
Part 2	1 VIAL, SINGLE-DOSE	5 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:68516-4605
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	250 [iU] in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4605-1	5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water injection

Product Information	
Item Code (Source)	NDC:68516-1001
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging				

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-1001-1	5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information

Product Type	PLASMA DERIVATIVE	Item Code (Source)	NDC:68516-4616

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4616-1	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	5 mL
Part 2	1 VIAL, GLASS	5 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:68516-4605

Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	250 [iU] in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4605-1	5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water solution

Product Information	
Item Code (Source)	NDC:76297-002
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76297-002-02	5 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4612

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4612-1	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts		
Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	5 mL
Part 2	1 VIAL, SINGLE-DOSE	5 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:68516-4606
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	500 [iU] in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4606-1	5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water injection

Product Information	
Item Code (Source)	NDC:68516-1001
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-1001-1	5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4617

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4617-1	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts		
Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	5 mL
Part 2	1 VIAL, GLASS	5 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:68516-4606
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	500 [iU] in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4606-1	5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water solution

Product Information	
Item Code (Source)	NDC:76297-002
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76297-002-02	5 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information

Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4613

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4613-2	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	10 mL
Part 2	1 VIAL, SINGLE-DOSE	10 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for

solution

Product Information	
Item Code (Source)	NDC:68516-4607
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	1000 [iU] in 10 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4607-2	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water injection

Product Information	
Item Code (Source)	NDC:68516-1002
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-1002-2	10 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4618

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4618-2	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL	10 mL
Part 2	1 VIAL, GLASS	10 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:68516-4607
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	1000 [iU] in 10 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4607-2	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water solution

Product Information	
Item Code (Source)	NDC:76297-002

Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76297-002-12	10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information

Product Type	PLASMA DERIVATIVE	Item Code (Source)	NDC:68516-4614

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4614-2	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	10 mL
Part 2	1 VIAL, SINGLE-DOSE	10 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:68516-4608
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	1500 [iU] in 10 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4608-2	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water injection

Product Information	
Item Code (Source)	NDC:68516-1002
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-1002-2	10 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4619

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4619-2	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL	10 mL

Part 2	1 VIAL, GLASS	10 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:68516-4608
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	1500 [iU] in 10 mL

Inactive Ingredients

Ingredient Name	Strength
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4608-2	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

Part 2 of 2

STERILE WATER

water solution

Product Information	
Item Code (Source)	NDC:76297-002
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:76297-002-12	10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		08/15/1978	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	08/15/1978	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4615

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4615-2	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL	10 mL
Part 2	1 VIAL, SINGLE-DOSE	10 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:68516-4610
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	2000 [iU] in 10 mL

Inactive Ingredients

Ingredient Name	Strength
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68516-4610-2	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	06/26/2014	

Part 2 of 2

STERILE WATER

water injection

Product Information	
Item Code (Source)	NDC:68516-1002
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-1002-2	10 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	06/26/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	06/26/2014	

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:68516-4620

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4620-2	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL	10 mL
Part 2	1 VIAL, GLASS	10 mL

Part 1 of 2

ALPHANATE

antihemophilic factor/von willebrand factor complex (human) injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:68516-4610
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX (UNII: 5T6B772R4Q) (HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX - UNII:5T6B772R4Q)	HUMAN COAGULATION FACTOR VIII/VON WILLEBRAND FACTOR COMPLEX	2000 [iU] in 10 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Albumin Human (UNII: ZIF514RVZR)	
arginine (UNII: 94ZLA3W45F)	
histidine (UNII: 4QD397987E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:68516-4610-2	10 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	06/26/2014	

Part 2 of 2

STERILE WATER

water solution

Product Information	
Item Code (Source)	NDC:76297-002
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
water (UNII: 059QF0KO0R) (Water - UNII:059QF0KO0R)	water	1 mL in 1 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:76297-002-12	10 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		06/26/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102475	06/26/2014	

Labeler - GRIFOLS USA, LLC (048987452)

Establishment

Name	Address	ID/FEI	Business Operations
Grifols Biologicals LLC		092694538	manufacture(68516-4611, 68516-4612, 68516-4613, 68516-4614, 68516-4615, 68516-4616, 68516-4617, 68516-4618, 68516-4619, 68516-4620)

Establishment

Name	Address	ID/FEI	Business Operations
Grifols Biologicals LLC		121076871	manufacture(68516-4611, 68516-4612, 68516-4613, 68516-4614, 68516-4615, 68516-4616, 68516-4617, 68516-4618, 68516-4619, 68516-4620)

Establishment

Name	Address	ID/FEI	Business Operations
LABORATORIOS GRIFOLS SA		463719725	manufacture(68516-1001, 68516-1002, 76297-002)

Revised: 6/2023

GRIFOLS USA, LLC