PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ALPHANATE®

Antihemophilic Factor / von Willebrand Factor Complex (Human)

Lyophilized powder for reconstitution and IV infusion

250 IU FVIII / 300 IU VWF (reconstitute with 5 mL diluent)
500 IU FVIII / 600 IU VWF (reconstituted with 5 mL diluent)
1000 IU FVIII / 1200 IU VWF (reconstituted with 10 mL diluent)
1500 IU FVIII / 1800 IU VWF (reconstituted with 10 mL diluent)
2000 IU FVIII / 2400 IU VWF (reconstituted with 10 mL diluent)

ATC Code B02BD06
Von Willebrand factor and coagulation factor VIII in combination

Manufactured by:
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ALPHANATE®

Antihemophilic Factor / von Willebrand Factor Complex (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous injection	lyophilized powder for reconstitution and injection 250 IU FVIII / 300 IU VWF 500 IU FVIII / 600 IU VWF 1000 IU FVIII / 1200 IU VWF 1500 IU FVIII / 1800 IU VWF 2000 IU FVIII / 2400 IU VWF	Human Albumin *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]), is a stable, sterile, purified lyophilized concentrate of the complex formed by Antihemophilic Factor (FVIII) (Human) and von Willebrand Factor (VWF) (Human). Each unit is provided with a pre-filled syringe of sterile water for injections, to reconstitute the product prior to administration.

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.

ALPHANATE contains human albumin as a stabilizer, and contains no preservatives.

INDICATIONS AND CLINICAL USE

ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]), is indicated for prevention and treatment of mild and/or non-life-threatening bleeding episodes or surgical bleeding in adult and pediatric patients with von Willebrand Disease (VWD), when desmopressin (DDAVP) is known or suspected to be either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

CONTRAINDICATIONS

ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- This product is prepared from human blood or plasma, it may potentially contain infectious agents
- May cause thromboembolic events to subjects treated with coagulation factor replacement therapy, especially in patients at risk for thrombosis

General

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps with capacity for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens and theoretically, the agent responsible for the Creutzfeldt-Jakob disease (CJD) or variant CJD, despite steps designed to reduce this risk.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV). The measures taken may be of limited value against parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular receipt of human plasma-derived factor VIII products.

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient.

Anaphylaxis and severe hypersensitivity reactions are possible. 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 treatment with ALPHANATE and administer appropriate emergency treatment should symptoms of anaphylaxis or severe hypersensitivity occur.

Cardiovascular

Thromboembolic events may occur in VWD patients receiving VWF/FVIII replacement therapy, especially in patients at risk for thrombosis. Caution should be exercised and appropriate measures should be considered in all VWD patients receiving VWF/FVIII replacement therapy, especially when additional thromboembolic risks exist.

Rapid administration may result in vasomotor reactions.

Hematologic
Intravascular hemolysis may occur with infusion of large doses of Antihemophilic Factor/von Willebrand Factor Complex, typically much larger doses than would be required for treatment of VWD. Should this condition occur and lead to progressive hemolytic anemia, discontinue administration of ALPHANATE and consider alternative therapy.

Immune
Patients who receive FVIII/VWF Complex (Human) may develop neutralizing antibodies (inhibitors) to either FVIII or VWF. Development of procoagulant activity-neutralizing antibodies (inhibitors) has been detected in patients receiving FVIII-containing products (References 4 and 5). No specific studies have been conducted with ALPHANATE to evaluate inhibitor formation. Carefully monitor patients for the development of VWF or FVIII inhibitors by appropriate clinical observations and laboratory tests. If following treatment with ALPHANATE, expected plasma VWF or FVIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures VWF or FVIII inhibitor concentrations.

Special Populations

Pregnant Women: 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.

Nursing Women: No human or animal data. Use only if clearly needed.

Pediatrics (< 18 years of age): The hemostatic efficacy of ALPHANATE has been studied in 18 pediatric subjects (ages 7-18) with von Willebrand Disease in the pivotal clinical trial. An additional 7 pediatric subjects (ages 3-17) were also included in a retrospective study evaluating the effectiveness of ALPHANATE in the perioperative prevention of excessive bleeding.

Geriatrics (> 65 years of age): Although some of the patients who participated in the ALPHANATE studies were > 65 years of age, no formal subgroup analyses were performed and therefore no safety or tolerability conclusions can be made for a geriatric population.

Monitoring and Laboratory Tests
Generally, 1 IU/kg VWF:RCo raises the circulating level of VWF:RCo by 2%. Levels of VWF:RCo of > 0.6 IU/ml (60%) and of FVIII:C of > 0.4 IU/ml (40%) should be achieved. In order to ensure these levels, regular monitoring of VWF:RCo and FVIII are recommended.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Allergic reactions (which may include angioedema, chest tightness, hypotension, rash, nausea, vomiting, paresthesia, restlessness, wheezing and dyspnea), have been observed with ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]). These may sometimes progress to anaphylaxis.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Clinical Trial Adverse Drug Reactions

Safety data were obtained from a single large prospective clinical trial with ALPHANATE in von Willebrand Disease involving 81patients being treated for bleeding episodes and/or prophylaxis prior to surgery. A retrospective chart review study for 39 patients with von Willebrand Disease was performed. Additionally, a post-market study in 23 patients for another indication, evaluating long-term safety has been conducted. The mean number of infusions was 53.0 ± 45.5 (median 42, range 2 - 160), and the mean number of months on the study was 10.2 ± 4.1 (median 10, range 2 - 17) for the repeated dose treatment. The results from these studies involved a total of 2116 infusions.

Table 1 - Adverse Drug Reactions from ALPHANATE Prospective Clinical Study

Preferred Term	Total Number and Percent of Subjects with an Adverse Event (N=81) N (%)
All body systems (Total)	12 (14.8)
Dizziness	3 (3.7)
Pruritus	3 (3.7)
Urticaria	3 (3.7)
Chills	2 (2.5)
Headache	2 (2.5)
Nausea	2 (2.5)
Rash	2 (2.5)
Vasodilation	2 (2.5)

Abnormal Hematologic and Clinical Chemistry Findings
Standard hematology and chemistry evaluations were performed in all clinical trials described above. There were no issues identified for any laboratory parameter in any of the studies, which was assessed as being related to treatment with ALPHANATE.

Post-Market Adverse Drug Reactions
There is over 40 years post-market experience with ALPHANATE and its predecessor products from the same manufacturer. The most common post-marketing ADRs reported include allergic/hypersensitivity reactions, nausea, fever, joint pain, fatigue, and infusion site pain. Adverse events reported in post-market usage have been consistent with those observed in the prospective clinical study.

DRUG INTERACTIONS

Drug-Drug Interactions
No interactions of human coagulation factor VIII or von Willebrand factor products with other medicinal products are known.

Drug-Food Interactions
Interactions of human coagulation factor VIII or von Willebrand factor products with foods have not been evaluated, but none are known or suspected.

Drug-Herb Interactions
Interactions of human coagulation factor VIII or von Willebrand factor products with herbs have not been evaluated, but none are known or suspected.

Drug-Laboratory Interactions
There were no issues raised for any laboratory parameters in any of the studies conducted with ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]).

Drug-Lifestyle Interactions
ALPHANATE has no or negligible influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations
For intravenous injection only, following reconstitution.

- Treatment with ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]) should be initiated under the supervision of a physician experienced in the treatment of hemostatic disorders.

- Generally, 1 IU/kg VWF:RCo raises the circulating level of VWF:RCo by 2%. Levels of VWF:RCo of > 0.6 IU/ml (60%) and of FVIII:C of > 0.4 IU/ml (40%) should be achieved.

- Each vial of ALPHANATE contains von Willebrand Factor:Ristocetin Cofactor (VWF:RCo), which is expressed on the label in International Units (IU) VWF:RCo/vial for the treatment of VWD. Additionally, ALPHANATE contains the antihemophilic factor (AHF) potency (FVIII:C activity) expressed on the label in IU FVIII/vial.

Recommended Dose and Dosage Adjustment

Prevention and treatment of hemorrhage or surgical bleeding in Patients with von Willebrand Disease

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 dose recommendations apply to both adult and pediatric patients.

Table 2 - ALPHANATE Dosing Guidelines for Patients with von Willebrand Disease

Indicated Use	VWF:RCo Dose	Target levels	Safety / Monitoring
Bleeding Episode – initial dose	40 to 60 IU/kg	80-120 mg/dL	Peak and trough activity levels of both FVIII:C and VWF:RCo should be taken at least once daily, and neither should exceed 150 IU/dL .
Bleeding Episode – subsequent doses *	40 - 60 IU/kg	80-120 mg/dL	
Surgical Prophylaxis (1 hour pre-op)	60 – 75 IU/kg	120-150 mg/dL	
Post-Operative*	40 – 60 IU/kg	80-120 mg/dL	

* additional doses should be re-administered based on clinical judgement at 12 - 24 hour intervals to maintain hemostasis until healing occurs. The dose and duration of the treatment depend on the clinical status of the patient, the type and severity of bleeding, and both VWF:RCo and FVIII:C levels. Dosing may be reduced in post-operative patients after the 3rd post-operative day.

Treatment guidelines above typically apply to all VWD types, although an initial dose of up to 80 IU/kg of VWF may be required, especially in patients with type 3 von Willebrand disease where maintenance of adequate levels may require greater doses than in other types of von Willebrand disease.

When using a FVIII-containing von Willebrand factor product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII:C. After 24 - 48 hours of treatment, reduced doses and/or prolongation of the dose interval or the use of a VWF product containing a low level of FVIII should be considered.

Missed Dose

If a patient being misses a dose, the missed dose should be taken as soon as possible, and then treatment should continue as before. If a dose is skipped, the next dose must usually not be doubled.

Administration

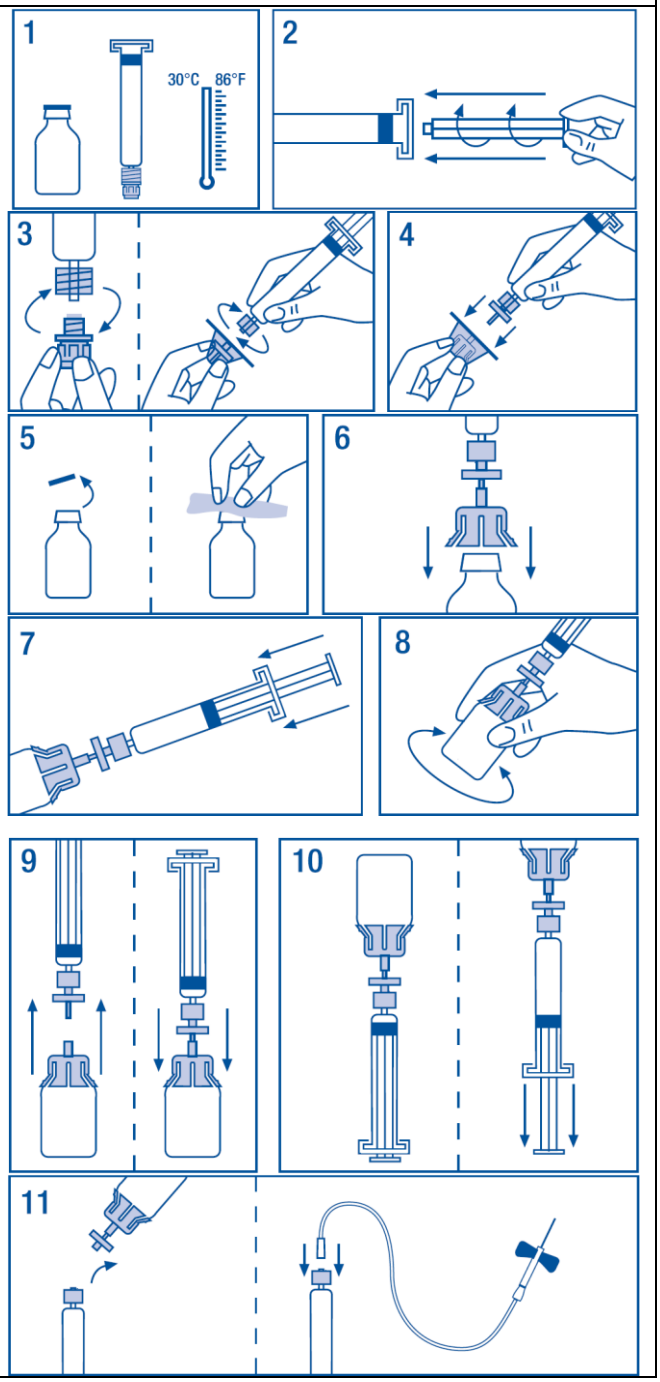
For intravenous use after reconstitution only.

- Use aseptic technique during reconstitution and administration.
- Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. The reconstituted ALPHANATE solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.
- Do not refrigerate after reconstitution. Store reconstituted ALPHANATE at room temperature (not to exceed 30 °C) prior to administration, and administer intravenously within three hours.
- Administer using suitable infusion needle.

- Do not administer ALPHANATE at a rate exceeding 10 mL/minute. Rapid administration of Factor VIII concentrates may result in vasomotor reactions.

Reconstitution:
To prepare the solution:

1. Warm the vial and syringe but not above 30 ºC.
2. Attach plunger to syringe containing solvent.
3. Remove filter from packaging. Remove cap from syringe tip and attach syringe to filter.
4. Remove vial adaptor from packaging and attach to syringe and filter.
5. Remove cap from vial and wipe stopper with a cleansing agent (like alcohol).
6. Pierce vial stopper with adaptor needle.
7. Transfer all solvent from syringe to vial.
8. Gently shake vial until all product is dissolved. Do not use if product is not properly dissolved or particles are visible.
9. Briefly separate the syringe/filter from vial/adaptor to release the vacuum.
10. Turn the vial upside down and draw the solution into the syringe.
11. Prepare injection site, separate syringe and inject product using suitable infusion needle (see important note below).



IMPORTANT:
When using the syringe with infusion systems or line extensions, please check the compatibility of the system. Adapters should be used when required to ensure proper administration of the

product.

After reconstitution with the Water for Injections solvent provided, the product should be used within 3 hours.

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

Table 3: ALPHANATE Formats Following Reconstitution:

Format	Volume of Diluent* to be Added to Vial*	Approximate Available Volume	Nominal Concentration per mL (VWF:RCo)
250 IU FVIII / 300 IU VWF	5 mL	5 mL	60 IU/mL
500 IU FVIII / 600 IU VWF	5 mL	5 mL	120 IU/mL
1000 IU FVIII / 1200 IU VWF	10 mL	10 mL	120 IU/mL
1500 IU FVIII / 1800 IU VWF	10 mL	10 mL	180 IU/mL
2000 IU FVIII / 2400 IU VWF	10 mL	10 mL	240 IU/mL

* diluent is sterile water for injection, EP (provided in prefilled syringe)

OVERDOSAGE

No symptoms of overdose with human VWF have been reported.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The von Willebrand Factor (VWF) is a large multimeric glycoprotein made in endothelial cells and megakaryocytes present in plasma and platelets. VWF performs three critical functions in primary hemostasis and in intrinsic blood coagulation, namely: (1) mediation of platelet adhesion at the site of vascular injury, (2) transportation of FVIII to sites where this factor participates in the coagulation process and (3) stabilization and protection of FVIII from *in vivo* proteolysis. Patients suffering from VWD have a deficiency or abnormality of VWF. A reduction in VWF concentration in the bloodstream results in low FVIII activity and abnormal platelet function. The result is that the platelets are prevented from adhering to sub-endothelial tissue, which can result in excessive bleeding.

In human plasma, VWF circulates as protein complex consisting of a molecule with coagulant activity (FVIII), which is non-covalently bound to the multimers of the VWF carrier protein. FVIII represents only about 1-2 % of the natural FVIII/VWF complex. Activated FVIII (FVIIIa) acts as a cofactor for activated factor IX (FIXa), accelerating the conversion of factor X to

activated factor X (FXa). FXa converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

The administration of VWF products re-establishes platelet-adhesion to the sub-endothelium at the site of vascular damage and aggregation of platelets, providing primary hemostasis. This effect occurs immediately, whereas the VWF-induced correction of the associated FVIII deficiency is delayed and progressive. Administered intravenously, VWF binds endogenous FVIII normally produced by the patient, and by stabilizing this factor, avoids its rapid degradation.

Pharmacodynamics

Von Willebrand disease (VWD) is an autosomal-inherited congenital bleeding disorder in which there is a deficiency or dysfunction of VWF as a result of missense and nonsense mutations in the gene encoding VWF. Patients with VWD that have quantitative or qualitative defects of VWF show impairment in both the primary phase of hemostasis and intrinsic blood coagulation. The main goal of treatment in VWD is to correct the dual hemostatic defect due to reduced or abnormal VWF that results in the deficiency of FVIII coagulant activity (FVIII:C) at the time of spontaneous bleeding or before an invasive procedure is performed.

VWF circulates in blood as a series of multimers ranging in size from 500 to 20,000 kDa. ALPHANATE is a FVIII/VWF complex preparation, which includes a range or multimers with molecular weights comparable to those in human plasma. Following infusion of ALPHANATE, 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.

Pharmacokinetics

Subjects received a single intravenous dose of ALPHANATE, 60 IU VWF:RCo/kg (75 IU VWF:RCo/kg in subjects younger than 18 years of age). Pharmacokinetic results from ALPHANATE in the 18 subjects are presented in Table 4.

The mean bleeding time (BT) prior to infusion was 29.2 ± 3.89 (range 13.5-30 minutes), with a median of 30 minutes. One hour post infusion, this was shortened to 10.4 ± 3.11 (range 6.0-16.0 minutes), with a median of 10.38 minutes.

Table 4: Summary of ALPHANATE Pharmacokinetic Parameters in Von Willebrand

Disease (N=18)

	VWF:RCo plasma level (mean % normal)[1]	FVIII :C plasma level (mean % normal)[1]	VWF:RCo $t_{½}$ (h)	FVIII :C $t_{½}$ (h)	VWF:RCo *in vivo* recovery	FVIII:C *in vivo* recovery
Single dose mean	206.0 ± 98.73	215.4 ± 86.25	7.5 ± 3.2 hours	21.5 ± 7.2 hours	3.1 ± 1.5 %/(IU/kg)	2.2 ± 0.6 %/(IU/kg)
Ranges:	87.0 - 440.0	110.0 - 421.0	5.9 to 9.1 hours	17.9 to 25.1 hours	1.3 - 5.7 %/(IU/kg)	1.3 - 3.3 %/(IU/kg)

1- assessed 15 minutes post-infusion

STORAGE AND STABILITY

ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]) and the solvent with which it is packaged for reconstitution should be stored at temperatures not exceeding 30 ºC. Do not freeze, as this may damage the diluent container, and compromise sterility.

Do not use beyond the expiry date noted on the label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]) is a white to slightly yellow freeze dried powder containing nominally 300, 600, 1200, 1800 or 2400 IU of human von Willebrand factor (VWF) per vial, and correspondingly, 250, 500, 1000, 1500 or 2000 IU of antihemophilic factor (FVIII) per vial.

The glass vials are made of Type I (USP) glass and closed with grey butyl rubber stoppers, aluminum crimp seal and plastic “flip-off” cover.

Each vial of ALPHANATE is supplied with a Type I glass syringe containing either 5 ml or 10 ml of Sterile Water for Injections (SWFI) Eur. Ph., for reconstitution of the dosage form.

Table 5: Available Dosage forms

Vial size (IU/vial) (FVIII:C / VWF:RCo)	Volume of SWFI Provided	Approximate volume after reconstitution	Concentration (IU/mL) (VWF:RCo)
250 IU / 300 IU	5 mL	5 mL	60 IU/mL
500 IU / 600 IU	5 mL	5 mL	120 IU/mL
1000 IU / 1200 IU	10 mL	10 mL	120 IU/mL
1500 IU / 1800 IU	10 mL	10 mL	180 IU/mL
2000 IU / 2400 IU	10 mL	10 mL	240 IU/mL

The other accessories supplied with ALPHANATE for reconstitution and administration of the product (for example, the vial adapter), are licensed medical devices in Canada and/or are

approved by Health Canada for distribution with ALPHANATE.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Antihemophilic Factor/von Willebrand Factor Complex (Human)

Molecular formula and molecular mass: Multimeric FVIII/VWF complex from 500 to 20,000 kDa

Physicochemical properties: Blood coagulation factor; ATC code: B02BD06

Product Characteristics

The active ingredient of ALPHANATE is Antihemophilic Factor and von Willebrand Factor Complex, which is derived from human plasma. Antihemophilic Factor (FVIII), is a heterologous glycoprotein required for the intrinsic pathway of blood coagulation, which results in the generation of thrombin and the fibrin clot. Von Willebrand Factor (VWF) co-purifies with Factor VIII as a FVIII/VWF complex. The VWF is a large, multimeric, adhesive glycoprotein that promotes platelet aggregation and platelet adhesion on damaged vascular endothelium and serves as a stabilizing carrier protein for Factor VIII.

ALPHANATE is obtained from source plasma through a purification process consisting of precipitation with polyethylene glycol (PEG) followed by affinity chromatography and precipitation with sodium chloride and glycine. These steps are designed to obtain a high purity FVIII/VWF complex concentrate. ALPHANATE is a sterile, lyophilized powder for injection and contains no preservatives or significant quantities of extraneous proteins such as fibrinogen or fibronectin. The final formulation contains albumin (human) and arginine as stabilizers, and histidine as a solubilizing agent.

Viral Inactivation capacity studies

The results of validation studies performed to determine virus clearance capacity associated with several steps in the manufacturing process of ALPHANATE are summarized below in Table 6. *In vitro* 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 Bovine Viral Diarrhea Virus (BVDV, a model for human Hepatitis C virus), and pseudorabies virus (PRV, a model for human hepatitis B and herpes viruses). *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), porcine parvovirus (PPV, a model for human Parvovirus B19), PRV, HIV-1 and BVDV. Precipitation with 3.5% polyethylene glycol (PEG) during the manufacturing process for ALPHANATE was also evaluated for virus elimination capability using HAV and PPV, as shown in Table 6.

Table 6: Estimation of the Overall Viral Clearance capacity (Log_{10} Reduction Factors) for ALPHANATE

Process steps	Log_{10} Reduction Factor				
	HIV-1	**PRV**	**BVDV**	**HAV**	**PPV**
3.5% PEG precipitation	n.d.	n.d.	n.d.	1.21	1.63
Solvent-Detergent	≥ 5.41	≥ 6.04	≥ 4.69*	n.a.	n.a.
Freeze drying + dry heat treatment	≥ 4.43	2.66	≥ 4.41	≥ 7.9	3.02
Total log_{10} Reduction Factor	**≥ 9.84**	**≥ 8.70**	**≥ 9.10**	**≥ 9.11**	**4.65**

≥: No residual infectivity detected. / nd: not done / na: not applicable, as the virus is resistant to this treatment

* Additional studies:The solvent-detergent step has also been validated for WNV, resulting in an inactivation capacity of ≥6.9 log_{10}/ml.

HIV: Human Immunodeficiency viruses
PRV: pseudorabies virus (model for hepatitis B and herpes viruses)
BVDV: Bovine Viral Diarrhea virus (model for Hepatitis C virus)
HAV: Hepatitis A virus
PPV: Porcine Parvovirus (model for Parvovirus B19)

Additionally, the manufacturing process was investigated for its capacity to remove infectivity of an experimentally spiked 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 experimentally spiked model agent. TSE reduction steps include: 3.5% polyethylene glycol precipitation (3.23 log_{10}), affinity chromatography (3.50 log_{10}) and saline precipitation (1.36 log_{10}). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

CLINICAL TRIALS

Study demographics and trial design

Table 7: Summary of patient demographics for clinical trials in Von Willebrand Disease

Study #	Trial design	Dosage, route of admin. and duration	Study subjects (n =)	Type of VWD (n =)	Mean age (Range)	Gender
ATC 93-01 - Part 1a	Open-label, multicenter PK study in VWD subjects - single dose and repeat dose	40 VWF:RCo IU/kg (50 IU/kg for subjects <18 yrs); IV; single dose	53 subjects	Type 1= 9 Type 2A=19 Type 2B= 1 Type 3= 22	33.9 years (7–75 yrs)	31 M / 50 F
ATC 93-01 - Part 1 (addendum)	Open-label, multicenter PK study in VWD subjects - cross-over comparison	60 VWF:RCo IU/kg (75 IU/kg for subjects <18 yrs); IV; single dose each of two products	18 subjects	Type 1= 3 Type 2A=3 Type 3= 12		
ATC 93-01 - Part 2a	Prospective, open-label, multicenter safety and efficacy study in VWD subjects with bleeding episodes	Mean dose 40.7±13.6 VWF:RCo IU/kg per IV infusion; mean 1.6±1.2 infusions per bleeding episode	14 subjects (with 87 bleeding episodes)	Type 1= 3 Type 2A=7 Type 3= 4		
ATC 93-01 - Part 2b	Prospective, open-label, multicenter safety and efficacy study in VWD subjects as prophylaxis prior to elective surgery	Median dose 60 VWF:RCo IU/kg (range: 20-76) for 1st IV infusion; Median dose 40 VWF:RCo IU/kg (range: 10-75) for 2nd IV infusion	39 subjects (with 71 procedures: 3 Major; 10 moderate, 58 minor)	Type 1= 6 Type 2A=17 Type 2B= 2 Type 3= 14		
IG-405	Retrospective; multi-center in VWD subjects treated for peri-operative bleeding prophylaxis	Mean dose 47.4 VWF:RCo IU/kg per IV infusion; mean 5.90±6.23 infusions per procedure	39 subjects (with 61 procedures)	Type 1= 18 Type 2= 12 Type 3= 9	39.2 years (3–72 yrs)	18 M / 21 F

A multi-part, open label, multicenter trial (ATC 93-01) was undertaken in 81 subjects with VWD (15 Type 1, 29 Type 2A, 5 Type 2B, 32 Type 3) in whom DDAVP was ineffective or contraindicated. The study included assessments of efficacy and safety among 14 subjects with VWD who were treated with ALPHANATE (antihemophilic factor/von Willebrand factor complex [human]) for 87 mild, non-life-threatening bleeding episodes, as well as assessments of efficacy and safety for 39 subjects with VWD who underwent 71 surgical procedures and were treated prophylactically with ALPHANATE. Pharmacokinetics of ALPHANATE were also

investigated. Dosing intervals of 23.8 ± 14.8 hours in treatment of bleeding, and 32.3 ± 56.4 hours in surgical prophylaxis were reported in the study.

Study IG-405 was a retrospective, multicenter study conducted in subjects with vWD who had been treated with ALPHANATE as perioperative prophylaxis against excessive bleeding in a total of 61 surgical or invasive procedures. The study included review of 63 procedures in 41 subjects, of which 61 procedures in 39 subjects were analyzed.

Study results

Table 8 - Results of study ATC 93-01 (Part 2a): Treatment of Minor Bleeding Episodes in Von Willebrand Disease Patients

Primary Endpoints	Protocol-specified target	Mean # infusions required per bleed episode (by VWD type)	Results
Control of the hemorrhage	≥75% subjects achieve hemostasis without use of alternate treatment	Type 1: 1.3 (±0.5) n= 4 episodes	100% subjects (87 bleed episodes) achieved bleeding control without alternate FVIII/VWF concentrate or cryoprecipitate for hemostasis
		Type 2: 1.3 (±0.9) n= 67 episodes	
		Type 3: 2.8 (±1.8) n= 16 episodes	

Table 9 - Results of study ATC 93-01 (Part 2b): Prophylaxis Prior to Elective Surgery in Von Willebrand Disease Patients

Primary Endpoints	Protocol-specified objective	Number of infusions	Results
Adequate hemostasis during healing; expected vs. actual blood loss	≥75% subjects not to exceed 1.5 times expected blood loss; postoperative control of bleeding without alternate treatment	31/71 (43.7%) procedures used 1 or 2 infusions Mean = 4.2 ±3.55 infusions (range 1 to 18)	Mean blood loss of 141.8 mL significantly less than 173.5 mL predicted (p<0.0001 Wilcoxon rank test). Bleeding no more than 50 mL over predicted in all but 3 subjects. Within 30 minutes of infusion, BT fully corrected in 25/63 (39.7%), partially corrected in 25/ 63 (39.7%) and demonstrated no correction in 12/63 (19%) evaluable procedures (no assessment in one case).

* BT= Bleed time

Table 10 - Results of study IG-405: Retrospective Assessment of Peri-operative Bleeding Prophylaxis in Von Willebrand Disease Patients

Primary Endpoints	Mean # infusions (total dose – VWF:RCo) by VWD type	Results
Treatment outcome rated using 4-point rating scale by investigator (Excellent; Good; Poor; None)	Type 1 (n=22 procedures) 7.14 (±7.78) infusions 18,541.5 (±18,879.9) IU*	Overall (N=61 procedures): 51 (83.6%) rated "Excellent" 7 (11.5%) rated "Good" 1 (1.6%) rated "Poor" 2 (3.3%) rated "none" Proportion of procedures with effective, vs. not effective rating (95.1% vs. 4.9%; p<0.0001**) Ratings by independent referee (2° endpoint) Proportion of procedures with effective, vs. not effective rating (91.8% vs. 8.2%; p<0.0001**)
	Type 2 (n=23 procedures) 5.09 (±4.13) infusions 19,755.5 (±17,912.9) IU*	
	Type 3 (n=16 procedures) 5.38 (±6.46) infusions 18,080.4 (±23,516.7) IU*	
	Total (n=61 procedures) 5.90 (±6.23) infusions 18,878.3 (±19,523.7) IU*	

* relative dose of VWF:RCo per infusion over all procedures was 47.4 IU/kg
** binomial test; H_0:<70% effective

DETAILED PHARMACOLOGY

Data from 39 subjects in Part 1a of ATC 93-01 (see Table 7) were considered evaluable. Results of the Bleed Time and plasma levels of vWF:RCo and FVlll:C at one hour post infusion of a single ALPHANATE dose (40 IU vWF:RCo/kg or 50 IU vWF:RCo/kg in pediatric subjects), are presented in Tabel 11.

Table 11 - Evaluation of Response at One Hour Post-Infusion

Variable/statistics		Infusions (N = 39)
RCo increased ≥50% of normal		
	Yes	38 (97.4%)
	No	1 (2.6%)
	Not applicable/missing	0 (0%)
FVIII:C increased ≥50% of normal		
	Yes	39 (100%)
	No	0 (0%)
	Not applicable/missing	0 (0%)
Full or partial correction of bleeding time		
	Yes	26 (66.7%)
	Full correction	9 (34.6%)
	Partial correction	17 (65.4%)
	No	12 (30.8%)
	Not applicable/missing	1 (2.6%)

The mean of half-life FVIII:C (39.7 hours), was substantially longer than the mean half-life of VWF:RCo (15.0 hours).

MICROBIOLOGY
Not applicable

TOXICOLOGY
No preclinical toxicity study was conducted for ALPHANATE.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

ALPHANATE®
(antihemophilic factor/von Willebrand factor complex [human])

Read this carefully before you start taking ALPHANATE and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ALPHANATE.

What is ALPHANATE used for?
ALPHANATE is used for prevention and treatment of mild and/or non-life-threatening bleeding episodes or surgical bleeding in adult and pediatric patients with von Willebrand Disease, when certain other medications are either not effective or cannot be used. It is not used for patients with severe VWD (Type 3) undergoing major surgery.

How does ALPHANATE work?
ALPHANATE is a highly purified concentrate of active human von Willebrand factor (VWF) and coagulation factor VIII (FVIII) complex. Patients suffering from von Willebrand Disease have a deficiency or abnormality of VWF. This deficiency in VWF results in lowered FVIII activity and abnormal function of platelets. Platelets are a part of your blood that are involved in the clotting process. When the platelets are not functioning correctly, the blood does not clot properly, which can result in excessive bleeding.

Administration of ALPHANATE restores the plasma levels of VWF to normal levels, so that the blood can clot.

What are the ingredients in ALPHANATE?
Medicinal ingredients: antihemophilic factor/von Willebrand factor complex (human)
Non-medicinal ingredients: albumin (human), arginine and histidine

ALPHANATE comes in the following dosage forms:
- 250 IU FVIII / 300 IU VWF dried powder in a vial
  (with a syringe containing 5 mL sterile water for injection, to make up the solution)
- 500 IU FVIII / 600 IU VWF dried powder in a vial
  (with a syringe containing 5 mL sterile water for injection, to make up the solution)
- 1000 IU FVIII / 1200 IU VWF dried powder in a vial
  (with a syringe containing 10 mL sterile water for injection, to make up the solution)
- 1500 IU FVIII / 1800 IU VWF dried powder in a vial
  (with a syringe containing 10 mL sterile water for injection, to make up the solution)
- 2000 IU FVIII / 2400 IU VWF dried powder in a vial
  (with a syringe containing 10 mL sterile water for injection, to make up the solution)

Do not use ALPHANATE if:

- You have previously suffered an allergic reaction when taking ALPHANATE, or if you know you are allergic to any of the ingredients or packaging components of ALPHANATE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALPHANATE. Talk about any health conditions or problems you may have, including if you:

- Have a history of deep vein thrombosis, stroke or other conditions involving blood clots
- Have a history hemolysis (a condition where your red blood cells break apart)
- Have previously developed inhibitors to ALPHANATE or another product like it (this is when the product stops working because your immune system makes antibodies against the medicine)
- Are pregnant or breastfeeding

Other warnings you should know about:

ALPHANATE is made from human plasma obtained from healthy donors. Plasma is a part of our blood. Like other biological products, it is theoretically possible that the product may contain viruses or other agents that can cause infection and illness. However, every donor and his/her donation are thoroughly screened to discard the presence of pathogens, and the processes used to make ALPHANATE are specifically designed with the ability to destroy or remove these agents if they were present. You should discuss the risks and benefits of this product with your healthcare provider.

Although there are no known interactions with ALPHANATE, be sure to tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

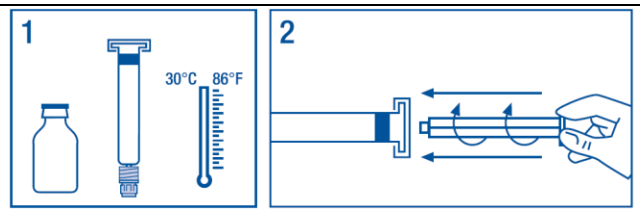
How to take ALPHANATE:

ALPHANATE is given as an intravenous administration. If you are administering the medication yourself, be sure to follow all instructions from your healthcare professional concerning the dose and timing of administrations.

Before being administered, the powdered ALPHANATE must be mixed with the sterile water that is provided in the package to create a liquid solution. Follow these instructions to prepare the solution.

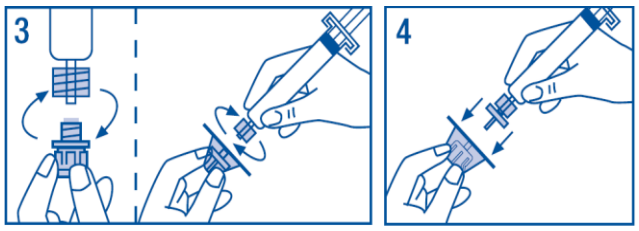
1. Warm the vial and syringe to room temperature (but not above 30 ºC)

2. Attach the plunger to the syringe containing the water.



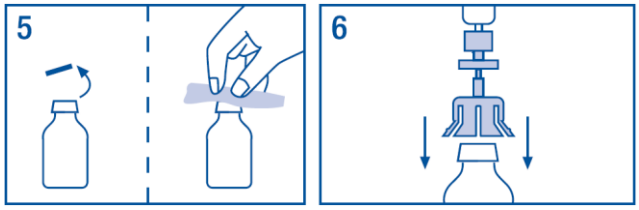
3. Remove filter from packaging. Remove cap from syringe tip and attach syringe to filter.

4. Remove vial adaptor from packaging and attach to syringe and filter.



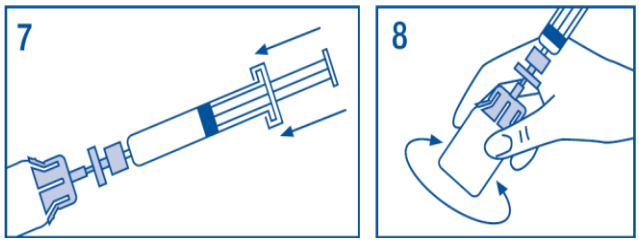
5. Remove cap from the vial and wipe rubber stopper with a cleaning agent (like alcohol).

6. Pierce the rubber stopper of the vial with the adaptor needle.



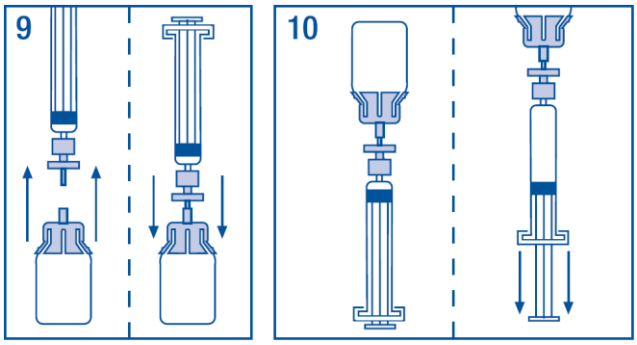
7. Transfer all sterile water from the syringe to the vial by pushing down the plunger.

8. Gently shake vial until all powder is dissolved. Do not use if the powder is not properly dissolved or if you can see particles in the solution.

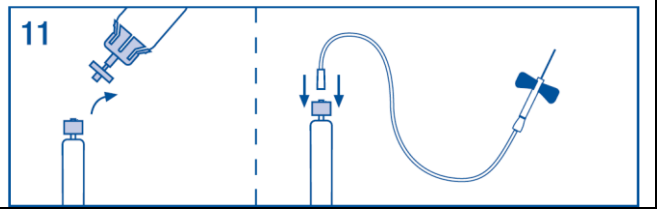


9. Briefly separate the syringe/filter from vial/adaptor. This will release the vacuum that is inside the vial. Then immediately reconnect the syringe/filter to the vial/adapter.

10. Turn the vial upside down and draw the solution into the syringe.



11. Separate the syringe from the filter/adapter/vial assembly. An infusion set can then be attached directly to the syringe containing the ALPHANATE solution. *



* IMPORTANT: only infusion devices that are compatible with the syringe should be used. Please verify this with your health care professional to ensure proper administration of the product.

Follow all instructions of your healthcare professional for safe administration of this product.

Usual dose:
Your doctor will tell you how much ALPHANATE to take. The dose will be different depending on your condition, and the type of bleeding event or surgical procedure involved.

Overdose:
There are no known symptoms of overdose with ALPHANATE.

If you think you have taken too much ALPHANATE, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, the missed dose should be taken as soon as possible, and then treatment should continue as before. If a dose is skipped, the next dose should not be doubled. Always seek and follow the advice of your Health Care Professional.

What are possible side effects from using ALPHANATE?
These are not all the possible side effects you may feel when taking ALPHANATE. If you experience any side effects not listed here, contact your healthcare professional.

The most frequent adverse drug reaction reported in clinical studies with ALPHANATE was itching of the skin (called pruritus). Even less frequently, there were reports of:

- rash
- pain (including headache and back pain)
- tingling sensation (like pins and needles; called paresthesia)
- dizziness
- respiratory distress
- nausea
- swelling of the face
- chills
- dilated blood vessels
- low blood pressure after standing up (called orthostatic hypotension).

The most common adverse drug events reported for ALPHANATE while it has been on the market are allergic (or hypersensitivity) reactions, nausea, fever, joint pain, fatigue, and pain at the infusion site. Allergic reactions may include swelling under the skin (like hives), chest tightness, low blood pressure, rash, nausea, vomiting, tingling sensation (like pins and needles), restlessness, wheezing and dyspnea. These may sometimes be serious, and you should immediately contact a healthcare professional if you believe you are having an allergic reaction.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
ALPHANATE should be stored in its original packaging at temperatures not exceeding 30 ºC. Do not freeze, since this might damage the syringe with the water. After a vial of ALPHANATE powder has been mixed with the water that was provided, it should be used right away (cannot be used after more than 3 hours). The mixed product should be kept at room temperature (do not refrigerate and keep below 30 ºC).

Keep out of reach and sight of children.

If you want more information about ALPHANATE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.grifols.ca, or by calling 1-866-482-5226.

This leaflet was prepared by Grifols Biologicals LLC

Last Revised: