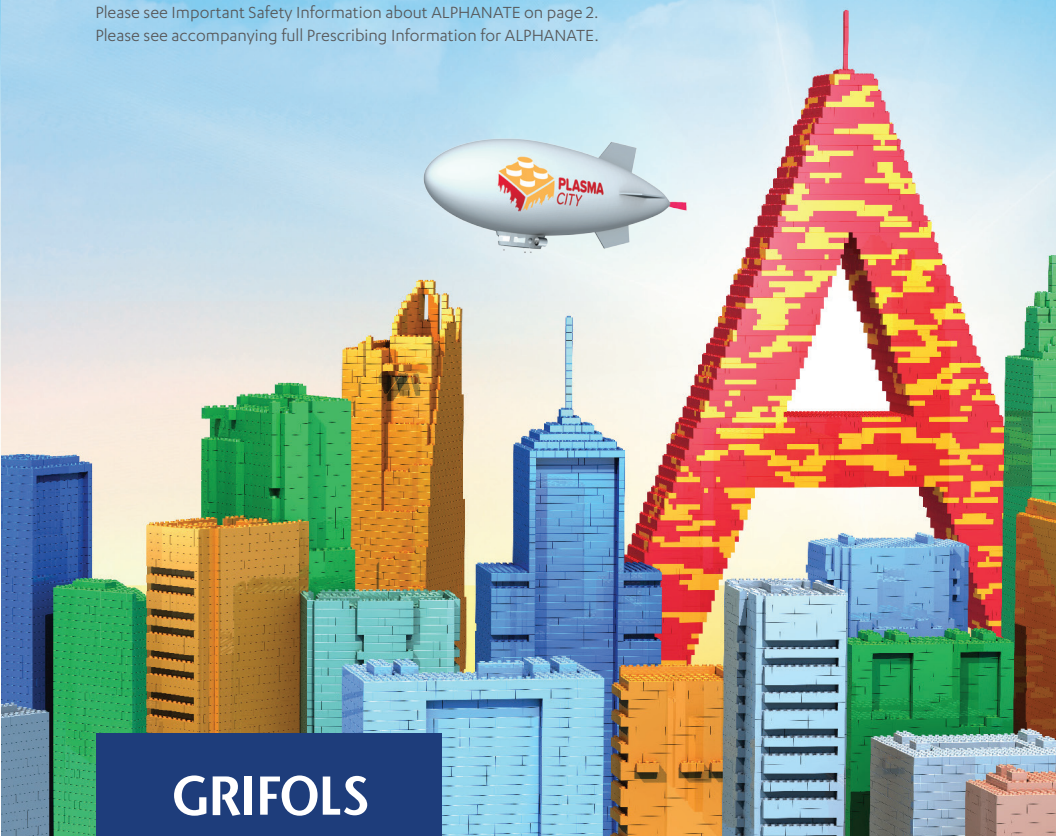
Alphanate®
antihemophilic factor/von Willebrand factor complex (human)

Welcome to Plasma City

A place where you can build your future with ALPHANATE

A plasma-derived treatment for patients with hemophilia A and von Willebrand disease

Please see Important Safety Information about ALPHANATE on page 2.
Please see accompanying full Prescribing Information for ALPHANATE.



GRIFOLS

Indications

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

IMPORTANT SAFETY INFORMATION

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

Anaphylaxis and severe hypersensitivity reactions are possible with ALPHANATE. Discontinue use of ALPHANATE if hypersensitivity symptoms occur, and initiate appropriate treatment.

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.

Thromboembolic events have been reported with AHF/VWF complex (human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may occur with infusion of large doses of AHF/VWF complex (human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

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.

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.

Please see accompanying full Prescribing Information for ALPHANATE.

Introduction

Welcome to Plasma City, your destination to learn more about ALPHANATE for your clotting disorder.

Many people with clotting disorders need replacement factor products to help manage their disease. This brochure provides information on ALPHANATE and the benefits and safety of human plasma-derived factor products.

Contents Page

Alphanate®
antihemophilic factor/von Willebrand factor complex (human)

WHAT IS ALPHANATE?

A human plasma-derived FVIII/VWF treatment

ALPHANATE is a natural, human plasma-derived factor product that contains both factor VIII (FVIII) and von Willebrand factor (VWF).[1] It is produced with a manufacturing process specifically designed to preserve FVIII and VWF together, the way they are found naturally in the body.

ALPHANATE is the only FDA-approved human plasma-derived FVIII/VWF treatment for adults and pediatric patients with hemophilia A or von Willebrand disease.*

ALPHANATE is a plasma-derived biotherapeutic product. All biotherapeutics—including plasma-derived, recombinant, transgenic, or gene therapy products—carry the same level of inherent pathogen transmission risk.

The ALPHANATE production process is designed to **PRESERVE FVIII AND VWF TOGETHER,** the way they are found naturally in the body.

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

ALPHANATE is manufactured by Grifols, a global leader in discovering, developing, and producing plasma-based therapies. At Grifols, we are committed to the highest standards of safety. Our products are made from plasma collected at centers that we own and operate across the United States.

***ALPHANATE 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.

Please see Important Safety Information on page 2 and see accompanying full Prescribing Information for ALPHANATE.

INHIBITORS ARE A SIGNIFICANT CHALLENGE

Inhibitors are the main treatment challenge today[2]

Inhibitors are antibodies that will develop in up to 35% of people with hemophilia A who are being treated with FVIII.[3] Inhibitors attach to the FVIII and impair its ability to stop bleeding.[4]

What affects your risk of inhibitors?

Anyone with hemophilia A can develop inhibitors at any time, but some genetic and environmental factors may affect a person's risk.

Genetic Factors	Environmental Factors
Severity of hemophilia A[4]	Intensive FVIII treatment at peak treatment moments[4]
Large mutation of the FVIII gene[4]	Early intensive exposure to FVIII treatment[5]
Family history of inhibitors[4]	Immunologic/inflammatory/infectious events (eg, vaccination, surgery, illness)[5]
Ethnicity[4]	Type of FVIII product used[3]

The good news is that inhibitors can be treated

While genetic factors cannot be changed, some environmental factors can be controlled, such as choice of treatment. For patients with inhibitors, treatment can require infusing very high volumes of FVIII. The goals of such treatment are to:

- Raise factor levels
- Decrease frequency or severity of bleeding
- Prevent bleeding complications

When FVIII and VWF are together, VWF may prevent inhibitors from binding to FVIII.[6]

FVIII=factor VIII; VWF=von Willebrand factor.

Alphanate®
antihemophilic factor/von Willebrand factor complex (human)

BENEFITS OF HUMAN PLASMA-DERIVED FVIII/VWF

Natural protection with FVIII and VWF[1]

In many patients with hemophilia A who have inhibitors, treatment goals can be met using a human plasma-based product that contains both FVIII and VWF. In fact, due to increased use in patients who have developed FVIII inhibitors, more human plasma-derived FVIII is used in the United States today than was used 15 years ago.

People with hemophilia A usually have enough VWF, and people with von Willebrand disease usually have enough FVIII.

So why give both factors together?

In the body, FVIII and VWF naturally travel together.[1]

VWF PROTECTS FVIII
from agents in the blood that try to destroy it.[7,8]

- VWF prolongs the half-life of FVIII, slows its breakdown, and helps it stay in the blood longer[8]
- VWF carries FVIII safely to the bleeding site where clotting is needed[9]
- VWF may prevent inhibitors from binding to FVIII, thus increasing the ability of FVIII to stop bleeding[6]

PRODUCTION AND SAFETY OF HUMAN PLASMA-DERIVED PRODUCTS

Plasma-derived clotting factors have come a long way

In the last 30 years, many scientific innovations have greatly increased the safety of human plasma-derived products. These innovations have increased the amount of confidence healthcare providers and patients have in the safety of human plasma-derived products. During the process of developing human plasma-derived products, including FVIII and VWF, 10 important steps are followed to help ensure the quality and safety of the final product.

These steps can be divided into 3 stages:

Because ALPHANATE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

FVIII=factor VIII; VWF=von Willebrand factor.

Please see Important Safety Information on page 2 and see accompanying full Prescribing Information for ALPHANATE.

DONOR SELECTION

Confidence starts with careful donor selection

The quality and safety of ALPHANATE begins with the collection of plasma, long before the manufacturing process even starts.

Each potential donor must pass 2 medical exams and 2 plasma tests over a 6-month period. If the donor passes, he or she then must pass a health screening at each visit as well as an annual physical exam. Each unit of plasma is tested after each collection using FDA protocols to verify the donor's health status and determine the safety of the collected plasma.

Not everyone can be a plasma donor
To qualify, donors must meet specific health requirements. Each time a donor comes to the collection center, he or she has a health screening and blood tests.

Plasma from one-time donors is *never* used to make ALPHANATE
Plasma collection from a new donor is kept in storage until he or she comes back for a second plasma collection and has another medical exam and blood tests. If a first-time donor does not return for a second donation within 6 months, the first donation is destroyed.

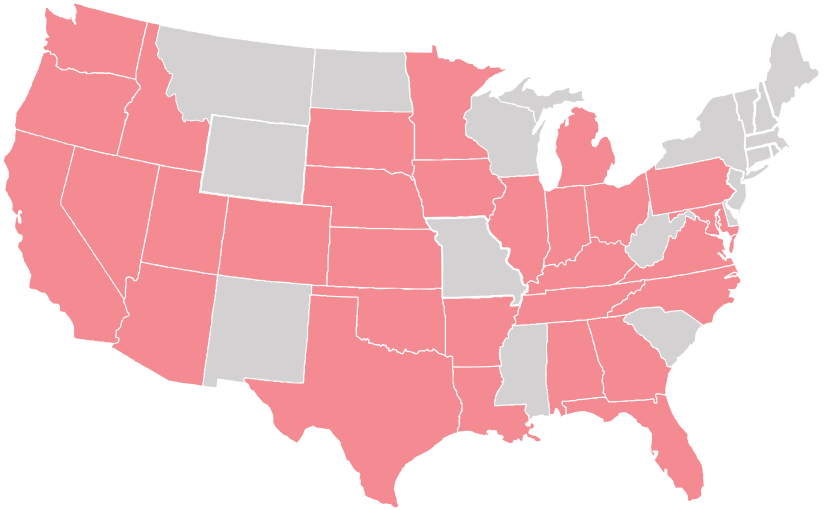
Each plasma donation has a unique barcode
This unique barcode makes it possible to trace each individual donation back to the donor.

All plasma donations are held for at least 60 days before being used
This way, if a donor later presents with any health issues, all plasma collected from that donor can be destroyed. You can feel confident in the plasma used to manufacture ALPHANATE because of the rigorous donor selection and plasma collection process.

The National Donor Deferral Registry
This comprehensive database lists the people who are permanently disallowed from donating plasma because they have tested positive for certain viruses. Every donor is checked against this computerized database each time plasma is collected, and this database is shared across all North American donor centers.

PLASMA COLLECTION

All plasma in Grifols products comes from a network of more than 160 FDA-inspected and -licensed donor centers in the United States



States with Grifols plasma donor centers

All plasma collected undergoes extensive, FDA-approved testing.
Grifols tests all plasma at its 2 state-of-the-art facilities in Texas.

Because ALPHANATE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

Please see Important Safety Information on page 2 and see accompanying full Prescribing Information for ALPHANATE.

MANUFACTURING

Each plasma donation goes through extensive laboratory testing before it is approved for use

After each unit of plasma is extensively analyzed using FDA-required safety protocols, the units are transferred to a Grifols manufacturing facility and then subjected to careful controls that protect their quality through a multiphase production process. During this time, fractionation takes place. During fractionation, clotting factors are separated from the rest of the plasma.

The factors then go through 2 more treatments specifically designed to inactivate or eliminate pathogens that still may be present.

Additional safety measures to inactivate/eliminate pathogens

Solvent/detergent treatment

Solvent/detergent is added to the factor to remove pathogens. Afterward, the solvent/detergent is removed from the factor so that it is not in the final product.

Dry heat treatment

After ALPHANATE is placed in the final container, it is freeze-dried and then heated in an oven at 80°C (176°F) for 72 hours. This step effectively eliminates pathogens.

ALPHANATE is the only product with FDA labeling for prion removal.

Since 1997,
THERE HAS NEVER BEEN A CONFIRMED CASE
of pathogen or prion transmission with ALPHANATE

The manufacturing process for ALPHANATE was investigated for the ability to decrease infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), a model for the CJD and vCJD agents. TSE reduction steps include: 3.5% polyethylene glycol precipitation, affinity chromatography, and saline precipitation.

These studies showed that even low levels of the vCJD and CJD infectious agents would be removed during manufacturing.

TRACKING FROM DONATION TO INFUSION

Each vial of ALPHANATE is laser etched so its origins can always be traced

Another feature that contributes to the safety of Grifols human plasma-derived products is the ability to trace plasma that has been collected from the donor center to the final product.

Each unit of plasma is coded and computer-traced throughout the collection, testing, and manufacturing processes.

This information is made available to healthcare providers using the PediGri® online system (www.pedigri.grifols.com).

To further enhance safety and deter tampering and counterfeiting, ALPHANATE has a laser-etched lot number on each vial and a holographic seal on each package.

ALPHANATE is the
ONLY FVIII PRODUCT WITH ONLINE TRACKING,
from plasma collection to final product.

Because ALPHANATE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

FVIII=factor VIII.

Please see Important Safety Information on page 2 and see accompanying full Prescribing Information for ALPHANATE.

THE GRIFOLS COMMITMENT TO SAFETY

Dedicated to patients for more than 75 years

ALPHANATE is manufactured by Grifols, a global leader in discovering, developing, and producing human plasma-based therapies. At Grifols, we are committed to the highest standards of safety. Safety is a core value for us—it is applied to everything we do, especially in the collection and manufacturing of our plasma-derived products.

For more than 70 years, Grifols has pioneered many of the methods used to collect human plasma and transform it into medicines for people who have hemophilia and other rare diseases, such as immune deficiencies and genetic emphysema.

Our manufacturing consistency and safety is achieved not only through testing the final product, but also by carefully controlling the manufacturing process from donor screening all the way to packaging.

Because ALPHANATE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

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

Please see Important Safety Information on page 2 and see accompanying full Prescribing Information for ALPHANATE.

THE CONVENIENCE OF ALPHANATE

Easy reconstitution and administration

The availability of a large 2000-IU vial size with low diluent volume may provide greater convenience in the form of:

- Less volume
- Fewer syringes
- Shorter daily infusion time

Among FVIII/VWF complex products, only ALPHANATE offers:

- Five convenient vial sizes with low diluent volumes

Potency	Diluent size
250 IU FVIII range	5 mL
500 IU FVIII range	5 mL
1000 IU FVIII range	10 mL
1500 IU FVIII range	10 mL
2000 IU FVIII range	10 mL

- Storage at room temperature for up to 3 years, so you don't need to worry about refrigeration

ALPHANATE also comes with an easy-to-use Mix2Vial®* needle-free reconstitution and transfer device in every carton.[1]

Alphanate®
antihemophilic factor/von Willebrand factor complex (human)

*Mix2Vial® is a registered trademark of Medimop Medical Projects, Ltd, a subsidiary of West Pharmaceutical Services, Inc.

FVIII=factor VIII; VWF=von Willebrand factor.

Alphanate®
antihemophilic factor/von Willebrand factor complex (human)

FOR PATIENTS WITH VON WILLEBRAND DISEASE

For patients with VWD, ALPHANATE:

- Is a high-purity product manufactured specifically to preserve the natural FVIII/VWF complex
- Has been approved and effectively used for VWD since 2007
- Has been used successfully as prophylaxis during surgery or invasive procedures
- Is indicated for use in both adults and children

ALPHANATE 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

Thromboembolic events have been reported with AHF/VWF complex (human) in VWD patients, especially in the setting of known risk factors.

ALPHANATE IS EFFECTIVE FOR VWD

Results from VWD clinical trials

In clinical trials of patients with VWD, ALPHANATE successfully prevented excessive bleeding during and immediately after a wide range of major and minor surgical and invasive procedures.[1]

In clinical trials, **more than 9 in 10 patients** had good or excellent results, meaning the bleeding was comparable to or only slightly worse than expected bleeding in patients without a clotting disorder[1]

Each vial of ALPHANATE lists both the FVIII and VWF units so you know exactly how much you are infusing.

FVIII IU	VWF IU*
250	300
500	600
1000	1200
1500	1800
2000	2400

*Average VWF content based on a ratio of 1.2:1

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.

VWD=von Willebrand disease; FVIII=factor VIII; VWF=von Willebrand factor.

Please see Important Safety Information on page 2 and see accompanying full Prescribing Information for ALPHANATE.

Factors for Health
Comprehensive Customer Focused Care

Factors for Health experts are here to talk to you one-on-one about benefits, savings options, and more

Factors for Health offers:

- The **$0 Copay Program**, wherein eligible patients or caregivers may pay as little as $0 for prescriptions*
- The **Free Trial Program** for eligible patients who are new to ALPHANATE
- **Benefits investigation and support** services to help you coordinate with your insurer
- The **Patient Assistance Program** for patients with no coverage or lapsed coverage
- **Care Coordination** to help you access and stay on ALPHANATE

To enroll, **CALL 844-MY-FACTOR (693-2286)**
Monday through Friday, 8:00 AM to 8:00 PM ET.

*Individual claims exceeding $2000 will be reviewed for network eligibility. Claims that are determined in-network will be approved and those determined to be out-of-network may be denied by the program administrator.

References: 1. ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) Prescribing Information. Grifols. **2.** Srivastava A, Brewer AK, Mauser-Bunschonten EP, et al; Treatment Guidelines Working Group. *Guidelines for the Management of Hemophilia*. 2nd ed. Montreal, Canada; World Federation of Hemophilia; 2012. **3.** Oldenburg J, Lacroix-Desmazes S, Lillicrap D. Alloantibodies to therapeutic factor VIII in hemophilia A: the role of von Willebrand factor in regulating factor VIII immunogenicity. *Haematologica*. 2015;100(2):149-156. **4.** DiMichele DM. *Inhibitors in Hemophilia: A Primer*. 4th ed. World Federation of Hemophilia; 2008. **5.** Carcao W, Re W, Ewenstein B. The role of previously untreated patient studies in understanding the development of FVIII inhibitors. *Haemophilia*. 2016;22(1):22-31. **6.** Di Minno G, Coppola A. A role for von Willebrand factor in immune tolerance induction in patients with haemophilia A and inhibitors? *Blood Transfus*. 2011;9(suppl 2):s14-s20. **7.** Franchini M, Lippi G. Von Willebrand factor-containing factor VIII concentrates and inhibitors in haemophilia A. *Thromb Haemost*. 2010;104:931-940. **8.** Federici AB, Mannucci PM. Management of inherited von Willebrand disease in 2007. *Ann Med*. 2007;39(5):346-358. **9.** Lacroix-Desmazes S, Navarrete A-M, André S, Bayry J, Kaveri SV, Dasgupta S. Dynamics of factor VIII interactions determine its immunologic fate in hemophilia A. *Blood*. 2008;112(2):240-249.

Thank you for visiting Plasma City

Remember, ALPHANATE is the #1 prescribed plasma-derived FVIII product* for the treatment of hemophilia A.

*Adapted from *The plasma proteins market in the United States 2014*. Revised 2015. Orange, CT: The Marketing Research Bureau, Inc.

FVIII=factor VIII.

Anaphylaxis and severe hypersensitivity reactions are possible with ALPHANATE. Discontinue use of ALPHANATE if hypersensitivity symptoms occur, and initiate appropriate treatment.

Because ALPHANATE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

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

Please see Important Safety Information on page 2 and see accompanying full Prescribing Information for ALPHANATE.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

GRIFOLS

March 2017 BN/A8/1216/0242