

- Pull back plunger drawing sufficient air into the syringe to allow reconstituted product to be withdrawn as described in the next step.
- Insert the spike end of the filter into the reconstituted concentrate vial. Inject air (Figure 2a) and withdraw the reconstituted product from the vial into the syringe (Figure 2b).

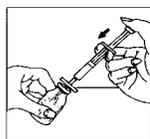


Figure 2a

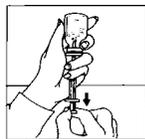


Figure 2b

- Remove the filter from the syringe; discard the filter and the empty concentrate vial, into the appropriate safety container. Attach syringe to an infusion set, expel air from the syringe and infusion set. Perform venipuncture and administer slowly at a rate not exceeding 10 mL/minute.
- If the patient is to receive more than one vial of concentrate, the infusion set will allow administration of multiple vials to be performed with a single venipuncture.
- Discard all administration equipment after use into the appropriate safety container. Do not reuse.

## HOW SUPPLIED

Alphanate® is supplied in sterile, lyophilized form in single dose vials accompanied by a suitable volume of diluent (Sterile Water for Injection, USP), according to AHF potency. Each vial is labeled with the Factor VIII:C potency expressed in AHF International Units. Alphanate® is packaged with a double-ended transfer needle and microaggregate filter for use in administration.

## STORAGE

Alphanate® should be stored at temperatures between 2 and 8 °C. Do not freeze to prevent damage to diluent vial. May be stored at room temperature not to exceed 30 °C for up to 2 months. When removed from refrigeration, record the date removed on the space provided on the carton.

## Rx only

## REFERENCES

- Fujimura, Y., Titani, K., Holland, L.Z., Roberts, J.R., Kostel, P., Ruggeri, Z.M., Zimmerman, T.S. A Heparin-Binding Domain of Human Von Willebrand Factor: Characterization and Localization to a Tryptic Fragment Extending from Amino Acid Residue Val-449 to Lys-728. *J Biol Chem* 1987, 262(4): 1734-1739.
- Hershgold, E.J. Properties of Factor VIII (Antihemophilic Factor). In: Spaet, T.H., ed. *Progress in Hemostasis and Thrombosis*, Grune and Stratton Publisher, 1974, 2:99-139.
- Ashenhurst, J.B., Langehenning, P.L., Seeler, R.A. Early Treatment of Bleeding Episodes with 10 U/Kg of Factor VIII. *Blood* 1977, 50:181.
- Data on file at Grifols Biologicals Inc.
- Edwards, C.A., Piet, M.P.J., Chin, S., Horowitz, B. Tri(n-Butyl) Phosphate/Detergent Treatment of Licensed Therapeutic and Experimental Blood Derivatives. *Vox Sang* 1987, 52:53-59.
- Horowitz, B. Investigations into the Application of Tri(n-Butyl) Phosphate/Detergent Mixture to Blood Derivatives. In: Morgenthaler, J.J., ed. *Viral Inactivation in Plasma Products*, Karger, 1989, 56:83-96.
- Eyster, M.E. Hemophilia: A Guide for the Primary Care Physician. *Postgraduate Medicine* 1978, 64:75-81.
- Biggs, R. Jaundice and Antibodies Directed Against Factors VIII and IX in Patients Treated for Haemophilia or Christmas Disease in the United Kingdom. *Br J Haematol* 1974, 26:313-329.
- Kasper, C.K., Kipnis, S.A. Hepatitis and Clotting Factor Concentrates. *JAMA* 1972, 221:510.
- Kasper, C.K. Incidence and Course of Inhibitors Among Patients with Classic Hemophilia. *Thromb Diath Haemorrh (Stuttg)* 1973, 30:263-271.
- Rizza, C.R., Biggs, R. The Treatment of Patients Who Have Factor VIII Antibodies. *Br J Haematol* 1973, 24:65-82.
- Roberts, H.R., Knowles, M.R., Jones, T.L., McMillan, C. The Use of Factor VIII in the Management of Patients with Factor VIII Inhibitors. In: Brinkhous, K.M., ed. *Hemophilia and New Hemorrhagic States*, International Symposium, New York, University of North Carolina Press, 1970, pp.152-163.
- Rizza, C.R., Biggs, R. Blood Products in the Management of Haemophilia and Christmas Disease. In: Poller, L., ed. *Recent Advances in Blood Coagulation*, Boston: Little Brown, 1969, pp.179-195.
- Hathaway, W.E., Mahasandana, C., Clarke, S. Alteration of Platelet Function After Transfusion in Hemophilia. *Proc 14th Ann Mtg, Am Soc Hematol* 1971, Abstracts, 58, No. 88.
- Shanbrom, E., Thelin, M. Experimental Prophylaxis of Severe Hemophilia with a Factor VIII Concentrate. *JAMA* 1969, 208(9):1853-1856.
- Levine, P.H. Hemophilia and Allied Conditions. In: *Current Therapy in Hematology-Oncology: 1983-1984*. Brain, M.C. (ed) New York: BC Decker, 1983, pp. 147-152.
- Kasper, C.K. Hemophilia and Hemophiloid Disorders. In: Conn, H.F., ed. *Current Therapy*, 4th ed., Philadelphia: Saunders, 1974, pp. 258-263.
- Kasper, C.K., Dietrich, S.L., Rapaport, S.I. Hemophilia Prophylaxis with Factor VIII Concentrate. *Arch Intern Med* 1970, 125:1004-1009.

Manufactured by:

**GRIFOLS**

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

Printed in USA  
Revised January 2004  
©2004

08-8150

# ANTIHEMOPHILIC FACTOR (HUMAN) ALPHANATE® Solvent Detergent / Heat Treated

## DESCRIPTION

Antihemophilic Factor (Human), Alphanate®, Solvent Detergent / Heat Treated, is a single dose, sterile, lyophilized concentrate of Factor VIII (AHF) intended for intravenous administration in the treatment of hemophilia A, or acquired Factor VIII deficiency.

Alphanate® is prepared from pooled human plasma by cryoprecipitation of the Factor VIII, fractional solubilization, and further purification employing heparin-coupled, cross-linked agarose which has an affinity to the heparin binding domain of vWf/FVIII:C complex.<sup>1</sup> The product is treated with a mixture of tri(n-butyl) phosphate (TNBP) and polysorbate 80 to reduce the risks of transmission of viral infection. In order to provide an additional safeguard against potential non-lipid enveloped viral contaminants, the product is also subjected to a 80 °C heat treatment step for 72 hours. However, no procedure has been shown to be totally effective in removing viral infectivity from coagulation factor products.

Alphanate® is labeled with the antihemophilic factor potency (Factor VIII:C activity) expressed in International Units (IU) per vial, which is referenced to the WHO International Standard.

Alphanate® contains Albumin (Human) as a stabilizer, resulting in a final container concentrate with a specific activity of at least 5 IU FVIII:C/mg total protein. Prior to the addition of the Albumin (Human) stabilizer, the specific activity is significantly higher.

When reconstituted with the appropriate volume of Sterile Water for Injection, USP, Alphanate® contains 0.3 - 0.9 g Albumin (Human)/100 mL; NMT 5 mmol calcium/L; NMT 750 µg glycine/IU FVIII:C; NMT 1.0 U heparin/mL; 10 - 40 mmol histidine/L; NMT 0.1 mg imidazole/mL; 50 - 200 mmol arginine/L; NMT 1.0 µg polyethylene glycol and polysorbate 80/IU FVIII:C; NMT 10 mEq sodium/vial; and NMT 0.1 µg TNBP/IU FVIII:C.

## CLINICAL PHARMACOLOGY

Antihemophilic Factor (Human) is a constituent of normal plasma and is required for clotting. The administration of Alphanate® temporarily increases the plasma level of this clotting factor, thus minimizing the hazard of hemorrhage.<sup>2,3</sup> Following the administration of Alphanate® during clinical trials, the mean *in vivo* half-life of Factor VIII observed in 12 adult subjects with severe hemophilia A was 17.9 ± 9.6 hours. In this same study, the *in vivo* recovery was 96.7 ± 14.5% at 10 minutes postinfusion.<sup>4</sup> Recovery at 10 minutes postinfusion was also determined as 2.4 ± 0.4 IU FVIII rise/dL plasma per IU FVIII infused/kg body weight.<sup>4</sup>

The solvent detergent treatment process has been shown by Horowitz, et al., to provide a high level of virus kill without compromising protein structure and function.<sup>3</sup> The susceptibility of human pathogenic viruses such as the human immunodeficiency viruses, hepatitis viruses, as well as marker viruses such as sindbis virus and vesicular stomatitis virus (VSV), to inactivation by organic solvent detergent treatment has been discussed in the literature.<sup>6</sup>

*In vitro* inactivation studies to evaluate the solvent detergent treatment step used in the manufacture of Alphanate® employed an assay with a sensitivity of 2 logs of virus for the marker viruses, vesicular stomatitis virus (VSV) and sindbis virus. The studies demonstrated a log kill of ≥4.1 for VSV and ≥4.7 for sindbis virus. Greater than or equal to 11.1 logs of HIV-1 and greater than or equal to 6.1 logs of HIV-2 were inactivated by the solvent detergent treatment step. The number of viral particles inactivated by the process represents the maximum amount of virus added initially to the sample, thus the results of the study indicate that all the added HIV virus was killed.<sup>4</sup>

In another study, the dry heat cycle of 80 °C for 72 hours of the Alphanate® manufacturing process was shown to inactivate greater than or equal to 5.8 logs of hepatitis A virus (HAV).

In a different study, the following steps in the manufacturing process of Alphanate® were evaluated for virus reduction/removal capability: precipitation with 3.5% polyethylene glycol (PEG), solvent detergent treatment with 0.3% tri-n-butyl phosphate and 1.0% polysorbate 80, heparin-actigel-ALD chromatography, lyophilization of Factor VIII and heat treatment at 80 °C for 72 hours. The following viruses were used in these studies: bovine herpes (BHV), bovine viral diarrhea virus (BVD), human poliovirus Sabin type 2 (POL), canine parvovirus (CPV) and human immunodeficiency virus, type 1 (HIV-1).

Table 1 summarizes the reduction factors for each virus evaluated for each viral inactivation/removal step validated in the manufacturing process of Alphanate®.<sup>4</sup>

However, no treatment method has yet been shown capable of totally eliminating all potential infective virus in preparations of coagulation factor concentrates.

Table 1

Virus Reduction (log <sub>10</sub> )	Processing Step					
	3.5% PEG Precipitation	Solvent Detergent treatment	Column chromatography	Lyophilization of Factor VIII	Dry heat Cycle (80 °C, 72h)	Total Log Removal
BHV	< 1.0	≥ 8.0	7.6	1.3	2.1	≥ 19.0
BVD	< 1.0	≥ 4.5	< 1.0	< 1.0	≥ 4.9	≥ 9.4
POL	3.3	-	< 1.0	3.4	≥ 2.5	≥ 9.2
CPV	1.2	-	< 1.0	< 1.0	4.1	5.3
VSV	-	≥ 4.1	-	-	-	≥ 4.1
Sindbis	-	≥ 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

## INDICATIONS AND USAGE

Antihemophilic Factor (Human), Alphanate<sup>®</sup>, is indicated for the prevention and control of bleeding in patients with Factor VIII deficiency due to hemophilia A or acquired Factor VIII deficiency.<sup>7</sup> No clinical trials have as yet been conducted using Alphanate<sup>®</sup> for treatment of von Willebrand's disease, therefore the product is not approved for this use.

## CONTRAINDICATIONS

None known.

## WARNINGS

Because Antihemophilic Factor (Human), Alphanate<sup>®</sup> is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma, through the application of viral elimination/reduction steps such as solvent detergent and heat treatment in the manufacturing process. Despite these measures, such products can still potentially transmit disease; therefore, the risk of infectious agents cannot be totally eliminated. All infections thought by a physician possibly to have been transmitted by this product should be reported to the manufacturer at 1-888-675-2762 (US) or 1-323-225-9735 (International). The physician should weigh the risks and benefits of the use of this product and should discuss these with the patient.

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C.<sup>8,9</sup> Incubation in a solvent detergent mixture during the manufacturing process is designed to reduce the risk of transmitting viral infection.<sup>8,9</sup> However, scientific opinion encourages hepatitis A and hepatitis B vaccinations for patients with hemophilia at birth or at the time of diagnosis.

## PRECAUTIONS

### General

Antihemophilic Factor (Human), Alphanate<sup>®</sup>, should not be administered at a rate exceeding 10 mL/minute. Rapid administration of a Factor VIII concentrate may result in vasomotor reactions.

Some patients develop inhibitors to Factor VIII. Factor VIII inhibitors are circulating antibodies (i.e., globulins) that neutralize the procoagulant activity of Factor VIII. No studies have been conducted with Alphanate<sup>®</sup> to evaluate inhibitor formation. Therefore, it is not known whether there are greater, lesser or the same risks of developing inhibitors due to the use of this product than there are with other antihemophilic factor preparations. Patients with these inhibitors may not respond to treatment with Antihemophilic Factor (Human), or the response may be much less than would otherwise be expected; therefore, larger doses of Antihemophilic Factor (Human) are often required. The management of bleeding in patients with inhibitors requires careful monitoring, especially if surgical procedures are indicated.<sup>10-12</sup>

Nursing personnel, and others who administer this material, should exercise appropriate caution when handling due to the risk of exposure to viral infection. Discard any unused contents into the appropriate safety container. Discard administration equipment after single use into the appropriate safety container. Do not resterilize components.

### Information for Patients

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

Some viruses, such as parvovirus B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect seronegative pregnant women, or immunocompromised individuals. The majority of parvovirus B19 and hepatitis A infections are acquired by environmental (natural) sources.

### Pregnancy Category C

Animal reproduction studies have not been conducted with Alphanate<sup>®</sup>. Therefore, it is not known whether it can cause fetal harm when administered to a pregnant woman or affect the reproductive capacity of a woman. Alphanate<sup>®</sup> should be given to a pregnant woman only if clearly needed.

### Pediatric Use

Clinical trials for safety and effectiveness in pediatric patients 16 years of age and younger have not been conducted. Across well controlled half-life and recovery clinical trial in patients previously treated with Factor VIII concentrates for Hemophilia A, the one pediatric patient receiving Alphanate<sup>®</sup> (solvent detergent) responded similarly when compared with 12 adult patients.<sup>4</sup> No adverse events were reported in either pediatric or adult patients with Alphanate<sup>®</sup>.<sup>4</sup>

## ADVERSE REACTIONS

Adverse reactions may include urticaria, fever, chills, nausea, vomiting, headache, somnolence, or lethargy.

Occasionally, mild reactions occur following the administration of Antihemophilic Factor (Human)<sup>13</sup>, such as allergic reactions, chills, nausea, or stinging at the infusion site. If a reaction is experienced, and the patient requires additional Antihemophilic Factor (Human), product from a different lot should be administered.

Massive doses of Antihemophilic Factor (Human) have rarely resulted in acute hemolytic anemia, increased bleeding tendency or hyperfibrinogenemia.<sup>14</sup> Alphanate<sup>®</sup> contains blood group specific isoagglutinins and, when large and/or frequent doses are required in patients of blood groups A, B, or AB, the patient should be monitored for signs of intravascular hemolysis and falling hematocrit. Should this condition occur, thus leading to progressive hemolytic anemia, the administration of serologically compatible type O red blood cells should be con-

sidered or the administration of Antihemophilic Factor (Human) produced from group-specific plasma should be considered.

## DOSAGE AND ADMINISTRATION

### For adult usage:

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

Antihemophilic factor potency (Factor VIII:C activity) is expressed in International Units (IU) on the product label. One unit approximates the activity in one mL of normal human plasma. Replacement therapy studies have shown a linear dose-response relationship with a 2.0-2.5% increase in Factor VIII activity for each unit of Factor VIII:C per kg of body weight transfused, from which an approximate factor of 0.5 IU/kg can be calculated.<sup>15,16</sup>

The following formula provides a guide for dosage calculation (the plasma Factor VIII may vary depending upon the age, weight, severity of hemorrhage, or surgical procedure of the patient):

Body weight (in kg)	X	0.50 IU/kg	X	Factor VIII Increase Desired (Percent)	=	Number of Factor VIII:C IU Required
Example: 50 kg	X	0.50 IU/kg	X	30 (% increase)	=	750 IU Factor VIII:C

Mild to moderate hemorrhages can usually be treated with a single administration of Alphanate<sup>®</sup> sufficient to raise the plasma Factor VIII level to 20 to 30%. In the event of more serious hemorrhage, the patient's plasma Factor VIII level should be raised to 30 to 50%. Infusions are generally required at twice daily intervals over several days.<sup>16</sup>

Surgery in patients with Factor VIII deficiency requires that postoperatively the Factor VIII level be raised to 50 to 80% and maintained at or above 30% for approximately two weeks. For dental extractions, the Factor VIII level should be raised to 50% immediately prior to the procedure; additional Alphanate<sup>®</sup> may be given if bleeding recurs.<sup>17</sup>

In patients with severe Factor VIII deficiency who experience frequent hemorrhages, Antihemophilic Factor (Human), Alphanate<sup>®</sup>, may be administered prophylactically on a daily or every other day schedule to raise the Factor VIII level to approximately 15%.<sup>18</sup>

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

**For pediatric usage: See PRECAUTIONS**

## RECONSTITUTION

### Always Use Aseptic Technique

1. Warm diluent (Sterile Water for Injection, USP) and concentrate (Alphanate<sup>®</sup>) to at least room temperature (but not above 37 °C).
2. Remove plastic caps from the diluent and concentrate vials.
3. Swab the exposed stopper surfaces with a cleansing agent such as alcohol. Do not leave excess cleansing agent on the stoppers.
4. Remove cover from one end of the double-ended transfer needle. Insert the exposed end of the needle through the center of the stopper in the DILUENT vial.
5. Remove plastic cap from the other end of the double-ended transfer needle now seated in the stopper of the diluent vial. To reduce any foaming, invert the vial of diluent and insert the exposed end of the needle through the center of the stopper in the CONCENTRATE vial at an angle, making certain that the diluent vial is always above the concentrate vial. The angle of insertion directs the flow of diluent against the side of the concentrate vial. Refer to Figure 1. There should be enough vacuum in the vial to transfer all of the diluent.

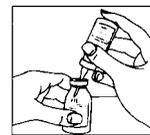


Figure 1

6. Disconnect the two vials by removing the transfer needle from the diluent vial stopper. Remove the double-ended transfer needle from the concentrate vial and discard the needle into the appropriate safety container.
7. Let the vial stand until contents are in solution, then GENTLY swirl until all concentrate is dissolved. Reconstitution requires less than 5 minutes.
8. DO NOT SHAKE THE CONTENTS OF THE VIAL. DO NOT INVERT THE CONCENTRATE VIAL UNTIL READY TO WITHDRAW CONTENTS.
9. Use as soon as possible after reconstitution.
10. After reconstitution, parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When reconstitution procedure is strictly followed, a few small particles may occasionally remain. The microaggregate filter will remove particles and the labeled potency will not be reduced.

## ADMINISTRATION BY SYRINGE

### Use Aseptic Technique

1. Peel cover from microaggregate filter package and securely install the syringe into the exposed Luer inlet of the filter, using a slight clockwise twisting motion.
2. Remove filter from packaging. Remove protective cover from the spike end of the filter.