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CSL Behring

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Important availability information for Antihemophilic Factor (Human) Monoclate-P® Factor VIII: C Pasteurized Monoclonal Antibody Purified

Dear Valued Customer:

Throughout CSL Behring's long history of providing leading hemophilia treatments, we have offered a broad portfolio of products, including Antihemophilic Factor (Human) Monoclate-P® Factor VIII:C Pasteurized Monoclonal Antibody Purified.

We are writing now to keep you updated about product availability. CSL Behring has made the difficult decision to discontinue Monoclate-P and we estimate that supply will be available through December 2018, giving you time to consider your patients' treatment options. Please note that due to expiration dating, availability of the 1500 IU vial size may be limited.

We recognize that Monoclate-P has been an important part of your patients' lives, and we remain committed to keeping you informed so you can appropriately advise them. We also want to share the rationale behind this decision. As hemophilia A treatment has advanced, and patients have transitioned from plasma-derived to recombinant and longer-acting therapies, it has been increasingly difficult to sustain the production and distribution of Monoclate-P.

We encourage your Monoclate-P patients to speak with their physician regarding treatment options. As a patient-focused company, CSL Behring strives to create innovative therapies for the hemophilia community. That's why we will continue to offer two therapies, AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, a next-generation Factor VIII therapy, and plasma-derived Antihemophilic Factor/von Willebrand Factor Complex (Human), Humate-P®.

With twice-weekly dosing available,* AFSTYLA is the first and only recombinant Factor VIII that delivers proven, long-lasting bleed protection with a novel single-chain design. AFSTYLA also delivered zero bleeds (median AsBR†) in all studied populations regardless of dosing regimen, as well as zero inhibitors in clinical trials with previously treated patients.

With AFSTYLA and Humate-P, all the support services your patients have come to rely on and trust with Monoclate-P will remain in place. AFSTYLA and Humate-P also use the Mix2Vial® system, which will keep their reconstitution process consistent.

CSL Behring is a company of CSL Limited.

*FDA approved for dosing 2 to 3 times a week.

†AsBR=annualized spontaneous bleeding rate in clinical trials (IQR=0–2.4 for patients ≥12 years; 0–2.2 for patients <12 years).

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As you evaluate the next steps in your Monoclate-P patients' therapy, we encourage you to consider AFSTYLA or Humate-P.

CSL Behring has provided Monoclate-P to patients for nearly three decades and we're committed to keeping you up to date with information on this important product going forward. If you have additional questions, a variety of resources are available:

- Contact your CSL Behring Representative
- Visit AFSTYLA.com for more information and to sign up for updates
- Visit Humate-P.com for more information and to sign up for updates
- Contact a My Source℠ Care Coordinator at 1-800-676-4266 Monday–Friday, 8 am to 8 pm ET

Please see Important Safety Information on pages 3–5 and accompanying full prescribing information for Monoclate-P, AFSTYLA, and Humate-P.

Sincerely,

Debra Bensen-Kennedy, MD
Vice President, North America Medical Affairs

Our Commitment

As with every therapy CSL Behring develops, AFSTYLA has the weight of our rigorous standards of quality behind it. Each step of the manufacturing process reflects that long-standing commitment to quality and safety.

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Important Safety Information for Monoclate-P

Monoclate-P®, Antihemophilic Factor (Human) Factor VIII: C Pasteurized Monoclonal Antibody Purified, is indicated for treatment of classical hemophilia (Hemophilia A). Affected individuals frequently require therapy following minor accidents. Surgery, when required in such individuals, must be preceded by temporary corrections of the clotting abnormality. Monoclate-P is not effective in controlling the bleeding of patients with von Willebrand's disease.

Monoclate-P is contraindicated in individuals with a known hypersensitivity to mouse protein. Products of this type are known to have caused allergic reactions, mild chills, nausea, or stinging at the infusion site. In some cases, inhibitors of Factor VIII may occur.

Monoclate-P is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

Please see full prescribing information for Monoclate-P.

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

Important Safety Information for AFSTYLA

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, is contraindicated in patients who have had life-threatening hypersensitivity reactions to AFSTYLA or its excipients, or to hamster proteins.

AFSTYLA is for intravenous use only. AFSTYLA can be self-administered or administered by a caregiver with training and approval from a healthcare provider or hemophilia treatment center. Higher and/or more frequent dosing may be needed for patients under 12 years of age.

Hypersensitivity reactions, including anaphylaxis, are possible. Advise patients to immediately report symptoms of a hypersensitivity reaction. If symptoms occur, discontinue AFSTYLA and administer appropriate treatment.

Development of Factor VIII (FVIII) neutralizing antibodies (inhibitors) can occur. If expected FVIII activity levels are not attained or bleeding is not controlled with appropriate dose, perform an assay to measure FVIII inhibitor concentration.

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Monitor plasma FVIII activity using a chromogenic assay or one-stage clotting assay. If one-stage clotting assay is used, multiply result by a conversion factor of 2 to determine FVIII activity level.

The most common adverse reactions reported in clinical trials (>0.5%) were dizziness and hypersensitivity.

AFSTYLA is indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes
- Routine prophylaxis to reduce frequency of bleeding episodes
- Perioperative management of bleeding

AFSTYLA is not indicated for the treatment of von Willebrand disease.

Please see full prescribing information for AFSTYLA.

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

Important Safety Information for Humate-P

Antihemophilic Factor/von Willebrand Factor Complex (Human), Humate-P® is indicated for treatment and prevention of bleeding in adult patients with hemophilia A (classical hemophilia). Humate-P is also indicated in adult and pediatric patients with von Willebrand disease (VWD) for (1) treatment of spontaneous and trauma-induced bleeding episodes, and (2) prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD, and patients with mild and moderate VWD for whom use of desmopressin is known or suspected to be inadequate. Humate-P is not indicated for the prophylaxis of spontaneous bleeding episodes.

Humate-P is contraindicated in individuals with a history of anaphylactic or severe systemic response to antihemophilic factor or von Willebrand factor preparations.

Monitor for intravascular hemolysis and decreasing hematocrit values in patients with A, B, and AB blood groups who are receiving large or frequent doses. Also monitor VWF:RCo and FVIII levels in VWD patients, especially those undergoing surgery.

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Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement. Caution should be exercised and antithrombotic measures considered, particularly in patients with risk factors for thrombosis.

Humate-P is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In patients receiving Humate-P in clinical studies for treatment of VWD, the most commonly reported adverse reactions (reported by >5% of subjects) were allergic-anaphylactic reactions, including urticaria, chest tightness, rash, pruritus, and edema. For patients undergoing surgery, the most common adverse reactions are postoperative wound or injection-site bleeding, and epistaxis.

Please see full prescribing information for Humate-P, including patient product information.

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

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Antihemophilic Factor (Human) Monoclate-P® Factor VIII:C Pasteurized Monoclonal Antibody Purified

℞ only

DESCRIPTION

Antihemophilic Factor (Human), Monoclate-P®, Factor VIII:C Pasteurized, Monoclonal Antibody Purified, is a sterile, stable, lyophilized concentrate of Factor VIII:C with reduced amounts of VWF:Ag and purified of extraneous plasma-derived protein by use of affinity chromatography. A murine monoclonal antibody to VWF:Ag is used as an affinity ligand to first isolate the Factor VIII Complex. Factor VIII:C is then dissociated from VWF:Ag, recovered, formulated and provided as a sterile lyophilized powder.[1,2,3] The concentrate as formulated contains Albumin (Human) as a stabilizer, resulting in a concentrate with a specific activity between 4 and 10 units/mg of total protein. In the absence of this added Albumin (Human) stabilizer, specific activity has been determined to exceed 3000 units/mg of protein.[4] Monoclate-P® has been prepared from pooled human plasma and is intended for use in therapy of classical hemophilia (Hemophilia A).

All Source Plasma used in the manufacture of this product was tested by FDA-licensed Nucleic Acid Testing (NAT) for HBV, HCV, and HIV-1 and found to be nonreactive (negative). This concentrate has been pasteurized by heating at 60°C for 10 hours in aqueous solution form during its manufacture in order to further reduce the risk of viral transmission.[5] However, no procedure has been shown to be totally effective in removing viral infectivity from coagulant factor concentrates (see **CLINICAL PHARMACOLOGY** and **WARNINGS**).

Monoclate-P® is a highly purified preparation of Factor VIII:C. When stored as directed, it will maintain its labeled potency for the period indicated on the container and package labels.[6,7]

Upon reconstitution of the 250, 500 and 1000 I.U. concentrates, a clear, colorless solution is obtained, containing 50 to 150 times as much Factor VIII:C as does an equal volume of plasma.

Upon reconstitution of the 1500 I.U. concentrate, a clear, colorless solution is obtained, containing 120 to 180 times as much Factor VIII:C as does an equal volume of plasma.

Each vial contains the labeled amount of antihemophilic factor (AHF) activity as expressed in terms of International Units (I.U.) of antihemophilic activity. One unit of antihemophilic activity is equivalent to that quantity of AHF present in one mL of normal human plasma. When reconstituted as recommended, the resulting solution contains approximately 300 to 450 millimoles of sodium ions per liter and has 2 to 3 times the tonicity of saline. It contains approximately 2-5 millimoles of calcium ions per liter, contributed as calcium chloride, approximately 1 to 2% Albumin (Human), 0.8% mannitol, and 1.2 mM histidine. The pH is adjusted with hydrochloric acid and/or sodium hydroxide. Monoclate-P® also contains trace amounts (≤50 ng per 100 I.U. of AHF) of the murine monoclonal antibody used in its purification (see **CLINICAL PHARMACOLOGY**).

Monoclate-P® is to be administered only intravenously.

CLINICAL PHARMACOLOGY

Factor VIII:C is the coagulant portion of the Factor VIII complex circulating in plasma. It is noncovalently associated with the von Willebrand protein responsible for von Willebrand factor activity. These two proteins have distinct biochemical and immunological properties and are under separate genetic control. Factor VIII:C acts as a cofactor for Factor IX to activate Factor X in the intrinsic pathway of blood coagulation.[8] Hemophilia A, a hereditary disorder of blood coagulation due to decreased levels of Factor VIII:C, results in profuse bleeding into joints, muscles or internal organs as a result of a trauma. Monoclate-P® provides an increase in plasma levels of AHF, thereby enabling temporary correction of Hemophilia A bleeding.

Clinical evaluation of Monoclate-P® concentrate for its half-life characteristics in hemophilic patients showed it to be comparable to other commercially available Antihemophilic Factor (Human) concentrates. The mean half-life obtained from six patients was 17.5 hours with a mean recovery of 1.9 units/dl rise/U/kg.

The pasteurization process used in the manufacture of this concentrate has demonstrated *in vitro* inactivation of human immunodeficiency virus (HIV) and several model viruses. In two separate studies, HIV was reduced by ≥7.0 $\log_{10}$ to an undetectable level and by 10.5 $\log_{10}$, respectively. In addition to HIV, studies were also performed using three lipid containing model viruses and one non-lipid, encapsulated model virus. Vesicular stomatitis (VSV) was reduced by ≥6.79 $\log_{10}$ to undetectable, Sindbis was reduced by ≥6.48 $\log_{10}$ to undetectable and Vaccinia was reduced by ≥5.36 $\log_{10}$ to undetectable. Murine encephalomyocarditis (EMC), a non-lipid, encapsulated model virus, was reduced by ≥7.1 $\log_{10}$ to undetectable.

Evidence of the capability of the purification and preparative steps used in the production of Monoclate-P® to reduce viral bioburden was obtained in studies involving the addition of known quantities of virus to cryoprecipitate. These studies were conducted using an earlier form of the concentrate which had not undergone liquid pasteurization (Antihemophilic Factor (Human), Monoclate®, Monoclonal Antibody Purified, Factor VIII:C, Heat-Treated). These studies provide evidence of the viral removal potential of the purification and preparative steps of the manufacturing process (exclusive of heat treatment) which are common to both concentrates. In one study, the viruses used were human immunodeficiency virus (HIV), Sindbis virus, vesicular stomatitis virus (VSV) and pseudorabies virus (PsRV). A comparison of the cumulative mean reductions for all viruses tested with the individual values obtained in each experiment indicates that the combined effects of the manufacturing steps, which purify the Factor VIII:C and prepare the concentrate in a final sterile container as a lyophilized powder, contribute viral reduction capabilities of approximately 5 to 6 logs. In a separate study, aluminum hydroxide treatment followed by antibody affinity chromatography reduced vaccinia virus infectivity by 4.81 logs. These studies indicate that the purification and preparative steps of the manufacturing process are capable of providing a non-specific, viral reduction of approximately 5 to 6 logs, independent of the pasteurization process.

Monoclate-P® contains trace amounts of mouse protein[9] (≤50 ng per 100 I.U. of AHF). In a study using an earlier form of the concentrate which had not undergone pasteurization (Monoclate®), a number of patients seronegative for Anti-HIV-1 were monitored to determine whether they would develop antibody or experience adverse reactions as a result of repeated exposure. These patients were treated on multiple occasions. Pre-study serum measurements of 27 patients for human anti-mouse IgG showed that, prior to treatment, 6 of them had either detectable antibody to mouse proteins or cross-reactive proteins. These patients continued to demonstrate similar or lower antibody levels during the study. Of the remaining 21 patients, 6 were shown to have low antibody levels on one or more occasions. In no case was observance of low antibody level associated with an anamnestic response or with any clinical adverse reaction. Patients were observed for time periods ranging from 2 to 30 months.

The viral safety of Monoclate-P® has been evaluated in two open-label studies using patients (aged 1 day to 20 years) with moderate to severe hemophilia A previously unexposed to blood or blood products. Thirty patients received Monoclate-P® therapy for 5 to 34 months as necessary according to the normal practices of the treatment center. These patients were followed for serum ALT elevations and a range of viral serologies. Six patients received another blood product prior to or during the study. Twenty-four patients were evaluable for assessment of viral safety of Monoclate-P®. No patients seroconverted to HIV, hepatitis nonA/nonB, or hepatitis B. Factor VIII:C inhibitors developed in 7 patients (23%) with 3 being high (>10 BU) titer.

INDICATIONS AND USAGE

Monoclate-P® is indicated for treatment of classical hemophilia (Hemophilia A). Affected individuals frequently require therapy following minor accidents. Surgery, when required in such individuals, must be preceded by temporary corrections of the clotting abnormality. Surgical prophylaxis in severe AHF deficiency can be accomplished with an appropriately-dosed pre-surgical IV bolus of Monoclate-P® followed by intermittent maintenance doses (see **DOSAGE AND ADMINISTRATION**).

Monoclate-P® is not effective in controlling the bleeding of patients with von Willebrand's disease.

CONTRAINDICATIONS

Known hypersensitivity to mouse protein is a contraindication to Monoclate-P®.

WARNINGS

Monoclate-P® is made from human blood. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Monoclate-P® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, 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 current viral infections and inactivating and/or removing certain viruses during manufacture (see **DESCRIPTION** section for viral reduction measures). The manufacturing procedure for Monoclate-P® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction step of the Monoclate-P® manufacturing process is the heat treatment of the purified, stabilized aqueous solution at 60°C for 10 hours. In addition, the purification procedure (several precipitation steps) used in the manufacture of Monoclate-P® also provides viral reduction capacity. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-866-915-6958 (in the U.S. or Canada).

Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see **Information For Patients**).

PRECAUTIONS

General - Most Antihemophilic Factor (Human) concentrates contain naturally occurring blood group specific antibodies. However, the processing of Monoclate-P® significantly reduces the presence of blood group specific antibodies in the final product. Nevertheless, when large or frequently repeated doses of product are needed, patients should be monitored by means of hematocrit and direct Coombs tests for signs of progressive anemia.

Formation of Antibodies to Mouse Protein - Although no hypersensitivity reactions have

been observed, because Monoclate-P® contains trace amounts of mouse protein (≤50 ng per 100 I.U. of AHF), the possibility exists that patients treated with Monoclate-P® may develop hypersensitivity to the mouse proteins.

Information For Patients - Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis, and should be advised to discontinue use of the concentrate and contact their physician 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 most seriously affects pregnant women, or immune-compromised individuals.

Although the overwhelming number of hepatitis A and parvovirus B19 cases are community acquired, there have been reports of these infections associated with the use of some plasma-derived products. Therefore, physicians should be alert to the potential symptoms of parvovirus B19 and hepatitis A infections and inform patients under their supervision receiving plasma derived products to report potential symptoms promptly.

Symptoms of parvovirus B19 include fever, drowsiness, chills and runny nose followed two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting and pain in the belly. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physicians if such symptoms occur.

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

Pediatric Use – The safety and effectiveness of Monoclate-P® for the treatment of hemophilia A has been demonstrated in 33 pediatric patients. As in adults, pediatric patients should be dosed based upon weight (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use - Clinical studies of Monoclate-P® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dosing should be appropriate to the clinical situation.

ADVERSE REACTIONS

Products of this type are known to cause allergic reactions, mild chills, nausea or stinging at the infusion site. In some cases, inhibitors of FVIII may occur.

DOSAGE AND ADMINISTRATION

Monoclate-P® is for intravenous administration only. As a general rule 1 unit of AHF activity per kg will increase the circulating AHF level by 2%.[10] The following formula[10] provides a guide of dosage calculations for both adult and pediatric patients:

Number of AHF I.U. Required	=	Body weight (in kg)	x	desired Factor VIII increase (% normal)	x	0.5

Although dosage must be individualized according to the needs of the patient (weight, severity of hemorrhage, presence of inhibitors), the following general dosages are suggested.[11]

1. MILD HEMORRHAGES - Minor hemorrhagic episodes will generally subside with a single infusion if a level of 30% or more is attained.
2. MODERATE HEMORRHAGE AND MINOR SURGERY - For more serious hemorrhages and minor surgical procedures, the patient's Factor VIII level should be raised to 30-50% of normal, which usually requires an initial dose of 15-25 I.U. per kg. If further therapy is required a maintenance dose is 10-15 I.U. per kg every 8-12 hours.
3. SEVERE HEMORRHAGE - In hemorrhages near vital organs (neck, throat, subperitoneal) it may be desirable to raise the Factor VIII level to 80-100% of normal which can be achieved with an initial dose of 40-50 I.U. per kg and a maintenance dose of 20-25 I.U. per kg every 8-12 hours.
4. MAJOR SURGERY - For surgical procedures a dose of AHF sufficient to achieve a level 80-100% of normal should be given an hour prior to surgery. A second dose, half the size of the priming dose, should be given five hours after the first dose. Factor VIII levels should be maintained at a daily minimum of at least 30% for a period of 10-14 days postoperatively. Close laboratory control to maintain AHF plasma levels deemed appropriate to maintain hemostasis is recommended.

Reconstitution

1. Warm both the diluent and Monoclate-P® in unopened vials to room temperature [not above 37°C (98°F)].
2. Remove the caps from both vials to expose the central portions of the rubber stoppers.
3. Treat the surface of the rubber stoppers with antiseptic solution and allow them to dry.
4. Using aseptic technique, insert one end of the double-end needle into the rubber stopper of the diluent vial. Invert the diluent vial and insert the other end of the double-end needle into the rubber stopper of the Monoclate-P® vial. Direct the diluent, which will be drawn in by vacuum, over the entire surface of the Monoclate-P® cake. (In order to assure transfer of all the diluent, adjust the position of the tip of the needle in the diluent vial to the inside edge of the diluent stopper.) Rotate the vial to ensure complete wetting of the cake during the transfer process.
5. Remove the diluent vial to release the vacuum, then remove the double-end needle, from the Monoclate-P® vial.
6. Gently swirl the vial until the powder is dissolved and the solution is ready for administration. The concentrate routinely and easily reconstitutes within one minute. To assure sterility, Monoclate-P® should be administered within three hours after reconstitution.
7. Parenteral drug preparations should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration

CAUTION: This kit contains two devices, a stainless steel 5 micron filter needle, individually labeled as a 5 micron filter needle and contained in a separate blister pack, and an all plastic 5 micron vented filter spike which is supplied with the four-item administration components blister pack, either of which may be used to withdraw the reconstituted product for administration. The withdrawal directions specific for each of these alternate devices must be followed exactly for whichever device is chosen for use as described below. Product loss or inability to withdraw product will result if the improper instructions are followed.

A. Administration using the stainless steel filter needle for withdrawal (This item is individually packaged in a separate, labeled blister pack.)

Intravenous Injection

Plastic disposable syringes are recommended with Monoclate-P® solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Using aseptic technique, attach the filter needle to a sterile disposable syringe.
2. Draw air into the syringe equal to or greater than the contents of the vial.
3. Insert the filter needle into the stopper of the Monoclate-P® vial, invert the vial, position the filter needle above the level of the liquid and inject all of the air into the vial.
4. Pull the filter needle back down below the level of the liquid until the tip is at the inside edge of the stopper.
5. Withdraw the reconstituted solution into the syringe being careful to always keep the tip of the needle below the level of the liquid.

CAUTION: Failure to inject air into the vial, or allowing air to pass through the filter needle while filling the syringe with reconstituted solution, may cause the needle to clog.

6. Discard the filter needle. Perform venipuncture using the enclosed winged needle with microbore tubing. Attach the syringe to the luer end of the tubing.

CAUTION: Use of other winged needles without microbore tubing, although compatible with the concentrate, will result in a larger retention of solution within the winged infusion set.

7. Administer solution intravenously at a rate (approximately 2 mL/minute) comfortable to the patient.

B. Administration using the all plastic vented filter spike for withdrawal (This spike is supplied in the four-item Administration Components pack.)

Intravenous Injection

Plastic disposable syringes are recommended with Monoclate-P® solution. The ground glass surfaces of all-glass syringes tend to stick with solutions of this type.

1. Using aseptic technique, attach the vented filter spike to a sterile disposable syringe.

CAUTION: DO NOT INJECT AIR INTO THE MONOCLATE-P® VIAL. The self-venting feature of the vented filter spike precludes the need to inject air in order to facilitate withdrawal of the reconstituted solution. The injection of air could cause partial product loss through the vent filter.

CAUTION: The use of other, non-vented filter needles or spikes without the proper procedure may result in an air lock and prevent the complete transfer of the concentrate.

2. Insert the vented filter spike into the stopper of the Monoclate-P® vial, invert the vial, and position the filter spike so that the orifice is at the inside edge of the stopper.
3. Withdraw the reconstituted solution into the syringe.
4. Discard the filter spike. Perform venipuncture using the enclosed winged needle with microbore tubing. Attach the syringe to the luer end of the tubing.

CAUTION: Use of other winged needles without microbore tubing, although compatible with the concentrate, will result in a larger retention of solution within the winged infusion set.

5. Administer solution intravenously at a rate (approximately 2 mL/minute) comfortable to the patient.

STORAGE

When stored at refrigerator temperature, 2-8°C (36-46°F), Monoclate-P® is stable for the period indicated by the expiration date on its label. Within this period, Monoclate-P® may be stored at room temperature not to exceed 25°C (77°F), for up to 6 months.

Avoid freezing which may damage container for the diluent.

HOW SUPPLIED

Monoclate-P® is supplied in a single dose vial with Sterile Water for Injection, USP, double-ended needle for reconstitution, vented filter spike for withdrawal, filter needle for withdrawal, winged infusion set and alcohol swabs. Factor VIII activity in IU is stated on the label of each vial.

Each product package consists of the following:

NDC Number	Approximate FVIII Activity (IU)	Component
0053-7631-02	250 (LOW)	Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7641-01], one 2.5 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-02], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.
0053-7632-02	500 (MID)	Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7642-01], one 5 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-05], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.
0053-7633-02	1000 (HIGH)	Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7643-01], one 10 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-10], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.
0053-7634-02	1500 (SUPER HIGH)	Carton (kit) containing one vial of Monoclate-P® [NDC 0053-7644-01], one 10 mL vial of Sterile Water for Injection, USP (diluent) [NDC 0053-7653-10], one double-ended needle for reconstitution, one vented filter spike for withdrawal, one filter needle for withdrawal, one winged infusion set, and alcohol swabs.

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Manufactured by:
CSL Behring LLC
Kankakee, IL 60901 USA
US License No. 1767

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AFSTYLA safely and effectively. See full prescribing information for AFSTYLA.

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain
Lyophilized Powder for Solution for Intravenous Injection
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain, is a recombinant, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes,
- Routine prophylaxis to reduce the frequency of bleeding episodes,
- Perioperative management of bleeding.

Limitation of Use

AFSTYLA is not indicated for the treatment of von Willebrand disease (1).

----------DOSAGE AND ADMINISTRATION----------

For intravenous use after reconstitution only.

- Each vial of AFSTYLA is labeled with the amount of recombinant Factor VIII in international units (IU or unit). One unit per kilogram body weight will raise the Factor VIII level by 2 IU/dL. (2.1)
- Plasma Factor VIII levels can be monitored using either a chromogenic assay or a one-stage clotting assay – routinely used in US clinical laboratories. **If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level.** (**2.1**, **5.3**)

Calculating Required Dose: (2.1)

Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Routine Prophylaxis: (2.1)

- Adults and adolescents (≥12 years): The recommended starting regimen is 20 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly.
- Children (<12 years): The recommended starting regimen is 30 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group.
- The regimen may be adjusted based on patient response.

Perioperative Management: (2.1)

- Ensure the appropriate Factor VIII activity level is achieved and maintained.

----------DOSAGE FORMS AND STRENGTHS----------

AFSTYLA is available as a white or slightly yellow lyophilized powder supplied in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 2500, or 3000 International Units (IU). (3)

----------CONTRAINDICATIONS----------

Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis to AFSTYLA or its excipients, or hamster proteins. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, immediately discontinue AFSTYLA and administer appropriate treatment. (5.1)
- Development of Factor VIII neutralizing antibodies (inhibitors) can occur. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. (5.2)
- If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported in clinical trials (>0.5% of subjects) were dizziness and hypersensitivity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch***.**

----------USE IN SPECIFIC POPULATIONS----------

- Pediatric: Clearance (based on per kg body weight) is higher in pediatric patients 0 to <12 years of age. Higher and/or more frequent dosing may be needed. (8.4)

See 17 for Patient Counseling Information and FDA-approved Patient Labeling.

Revised: September 2017R

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CSL Behring
FULL PRESCRIBING INFORMATION

AFSTYLA®

Antihemophilic Factor (Recombinant), Single Chain

For Intravenous Injection, Powder and Solvent for Injection

1 INDICATIONS AND USAGE

AFSTYLA®, Antihemophilic Factor (Recombinant), Single Chain is a recombinant, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes,
- Routine prophylaxis to reduce the frequency of bleeding episodes,
- Perioperative management of bleeding.

Limitation of Use

AFSTYLA is not indicated for the treatment of von Willebrand disease.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dosing Guidelines

- Dose and duration of treatment depend on the severity of the Factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition.
- Each vial of AFSTYLA states the actual amount of Factor VIII activity in International Units (IU) as determined by chromogenic assay. One IU corresponds to the activity of Factor VIII contained in 1 milliliter (mL) of normal human plasma.
- Plasma Factor VIII levels can be monitored using either a chromogenic assay or a one-stage clotting assay – routinely used in US clinical laboratories. If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level [see *Warnings and Precautions (5.3)*].

Calculating Required Dose

- The calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU Factor VIII per kg body weight raises the plasma Factor VIII level by 2 IU/dL. The expected in vivo peak increase in Factor VIII level expressed as IU/dL (or % of normal) is estimated using the following formula:

Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

The dose to achieve a desired in vivo peak increase in Factor VIII level may be calculated using the following formula:

Dose (IU) = body weight (kg) x Desired Factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

The amount of AFSTYLA to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

On-demand Treatment and Control of Bleeding Episodes

A guide for dosing AFSTYLA in the treatment and control of bleeding episodes is provided in Table 1. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

Table 1. Dosing for On-demand Treatment and Control of Bleeding Episodes

Type of Bleeding Episode	Factor VIII Activity Level Required (% or IU/dL)	Frequency of Doses (hours)
Minor Uncomplicated hemarthrosis, minor muscle bleeding or oral bleeding	20-40	Repeat injection every 12-24 hours until the bleeding is resolved.
Moderate Muscle bleeding (except iliopsoas), hemarthrosis, or mild trauma	30-60	Repeat injection every 12-24 hours until the bleeding is resolved.
Major/Life-threatening Limb threatening hemorrhage, deep muscle bleeding (including iliopsoas), intracranial and retropharyngeal bleeding, fractures or head trauma	60-100	Repeat injection every 8-24 hours until bleed is resolved.

Routine Prophylaxis

- Adults and adolescents (≥12 years): The recommended starting regimen is 20 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly.
- Children (<12 years): The recommended starting regimen is 30 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group [see *Clinical Pharmacology (12.3)*].
- The regimen may be adjusted based on patient response.

Perioperative Management of Bleeding

A guide for dosing AFSTYLA during surgery (perioperative management of bleeding) is provided in Table 2. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

Table 2. Target Factor VIII Activity Levels for Perioperative Management of Bleeding

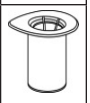
Type of Surgery	Factor VIII Activity Level Required (% or IU/dL)	Frequency of Doses (hours) / Duration of Therapy (days)
Minor (including tooth extraction)	30-60	Repeat injection every 24 hours for at least 1 day, until healing is achieved.
Major (intracranial, intra-abdominal, intrathoracic, or joint-replacement)	80-100	Repeat injection every 8-24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a Factor VIII activity of 30-60% (IU/dL).

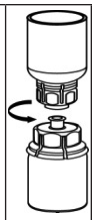
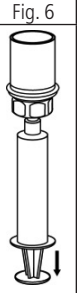
2.2 Preparation and Reconstitution

- Reconstitute AFSTYLA using aseptic technique with diluent provided in the kit.
- Visually inspect the reconstituted solution for particulate matter prior to administration. The solution should be free from visible particles. Do not use if particulate matter is observed.

The procedures provided in Table 3 are general guidelines for the preparation and reconstitution of AFSTYLA.

Table 3. AFSTYLA Reconstitution Instructions

1.	Ensure that the AFSTYLA vial and diluent vial are at room temperature. Prepare and administer using aseptic technique.	
2.	Place the AFSTYLA vial, diluent vial, and Mix2Vial® transfer set on a flat surface.	
3.	Remove AFSTYLA and diluent vial flip caps. Wipe the stoppers with the sterile alcohol swab provided and allow the stoppers to dry prior to opening the Mix2Vial transfer set package.	
4.	Open the Mix2Vial transfer set package by peeling away the lid (Fig. 1). Leave the Mix2Vial transfer set in the clear package.	 Fig. 1
5.	Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Fig. 2).	 Fig. 2
6.	Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, not the Mix2Vial transfer set (Fig. 3).	 Fig. 3
7.	With the AFSTYLA vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the AFSTYLA vial (Fig. 4). The diluent will automatically transfer into the AFSTYLA vial.	 Fig. 4
8.	With the diluent and AFSTYLA vial still attached to the Mix2Vial transfer set, gently swirl the AFSTYLA vial to ensure that the AFSTYLA is fully dissolved (Fig. 5). Do not shake the vial.	 Fig. 5

9. With one hand, grasp the AFSTYLA side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set, and unscrew the set into two pieces. (Fig. 6).	 Fig. 6
10. Draw air into an empty, sterile syringe. While the AFSTYLA vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the AFSTYLA vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly. (Fig. 7).	 Fig. 7
11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Fig. 8).	 Fig. 8
12. After reconstitution, infuse immediately or within 4 hours. Reconstituted AFSTYLA may be stored at room temperature, not to exceed 25°C (77°F), for up to 4 hours. Do not freeze. Protect from direct sunlight.	
13. Record treatment - Remove the peel-off portion of the label from each vial used, and affix it to the patient's treatment diary/log book or scan the vial if recording the infusion electronically.	
14. If the dose requires more than one vial, use a separate, unused Mix2Vial® transfer set for each product vial. Repeat step 10 to pool the contents of the vial into one syringe.	

2.3 Administration

- Use aseptic technique when administering AFSTYLA.
- Do not mix AFSTYLA with other medicinal products.
- Administer by intravenous injection. The rate of administration should be determined by the patient's comfort level. Do not exceed infusion rate of 10 mL per minute.
- Administer AFSTYLA at room temperature within 4 hours after reconstitution.
- AFSTYLA is for single use only. Following administration, discard any unused solution and all administration equipment in an appropriate manner as per local requirements.
- If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

3 DOSAGE FORMS AND STRENGTHS

AFSTYLA is available as a white or slightly yellow lyophilized powder supplied in single-use vials containing nominally 250, 500, 1000, 1500, 2000, 2500, or 3000 IU. The actual potency is labeled on each AFSTYLA vial and carton.

4 CONTRAINDICATIONS

AFSTYLA is contraindicated in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis to AFSTYLA or its excipients (e.g., polysorbate 80) *[see Description (11)]*, or hamster proteins *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible with AFSTYLA. Inform patients of the early signs of hypersensitivity reactions that may progress to anaphylaxis (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and pruritus). Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

For patients with previous hypersensitivity reactions, consider premedication with antihistamines.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of Factor VIII products. Monitor patients for the development of neutralizing antibodies (inhibitors) by appropriate clinical observations and laboratory tests. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled after AFSTYLA administration, the presence of an inhibitor (neutralizing antibody) should be suspected *[see Warnings and Precautions (5.3)]*.

Contact a specialized hemophilia treatment center if a patient develops an inhibitor.

5.3 Monitoring Laboratory Tests

- Monitor plasma Factor VIII activity in patients receiving AFSTYLA using either the chromogenic assay or the one-stage clotting assay, which is routinely used in US clinical laboratories. The chromogenic assay result most accurately reflects the clinical hemostatic potential of AFSTYLA and is preferred. The one-stage clotting assay result underestimates the Factor VIII activity level compared to the chromogenic assay result by approximately one-half. If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level. Incorrect interpretation of the Factor VIII activity obtained by the one-stage clotting assay could lead to unnecessary additional dosing, higher chronic dosing, or investigations for an inhibitor.
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected plasma Factor VIII activity levels are not attained or if bleeding is not controlled with the expected dose of AFSTYLA. Use Bethesda Units (BU) to report inhibitor levels.

6 ADVERSE REACTIONS

The most common adverse reactions (>0.5% of subjects) reported in clinical trials were dizziness and hypersensitivity.

6.1 Clinical Trials Experience

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

The safety, efficacy and pharmacokinetics of AFSTYLA have been evaluated in 258 previously treated patients (PTPs) with severe hemophilia A (<1% endogenous Factor VIII activity) who received at least one dose of AFSTYLA as part of either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management in two completed clinical trials (an adult/adolescent study [≥12 to 65 years of age] and a pediatric study [<12 years of age]), and an ongoing extension study (0 to ≤65 years of age). Patients with a history of, or current FVIII inhibitors, or any first order family history of FVIII inhibitors, patients with known hypersensitivity (allergic reaction or anaphylaxis) to any FVIII product or hamster protein, and patients with evidence of thrombosis, including deep vein thrombosis, stroke, pulmonary embolism, myocardial infarction and arterial embolus within 3 months prior to Day 1 of the study were excluded from study participation.

Eighty-four (32.6%) subjects were children <12 years of age (35 [13.6%] 0 to <6 years and 49 [19.0%] ≥6 to <12 years), 14 (5.4%) were adolescents (≥12 to <18 years), and 160 (62.0%) were adults (≥18 to ≤65 years). There have been a total of 28,418 exposure days (EDs), with at least 28,492 injections of AFSTYLA administered. In the completed studies, a total of 185 subjects achieved at least 50 EDs, of whom 60 subjects achieved ≥100 EDs.

Adverse reactions (ARs) (summarized in Table 4) were reported for 14 of 258 (5.4%) subjects in all studies. An adverse reaction of hypersensitivity resulted in the withdrawal of one subject. No subject developed neutralizing antibodies (inhibitors) to Factor VIII or antibodies to host cell proteins. No events of anaphylaxis or thrombosis were reported.

Table 4. Adverse Reactions Reported for AFSTYLA (N=258)

MedDRA System Organ Class	Adverse Reactions	Number of Subjects n (%)
Immune system disorders	Hypersensitivity	4 (1.6)
Nervous system disorders	Dizziness	2 (0.8)
	Paresthesia	1 (0.4)
Skin and subcutaneous tissue disorders	Rash	1 (0.4)
	Erythema	1.(0.4)
	Pruritus	1 (0.4)
General disorders and administration site conditions	Pyrexia	1 (0.4)
	Injection-site pain	1 (0.4)
	Chills	1 (0.4)
	Feeling hot	1 (0.4)

6.2 Immunogenicity

All subjects were monitored for inhibitory and binding antibodies to AFSTYLA, and binding antibodies to CHO host cell proteins prior to the first infusion of AFSTYLA, at defined intervals during the studies and at the end of study visit.

Preliminary data from an actively enrolling clinical trial in previously untreated patients (PUPs) aged ≤5 years indicate that 6 of 15 treated subjects (40% with a 95% confidence interval of 16%, 68%) developed an inhibitor. Of these, 3 subjects (20%) had peak inhibitor values in the high titer range, and 3 subjects (20%) had peak values in the low titer range. Of the 6 subjects who tested positive for inhibitors, 5 subjects have remained in the trial and have continued treatment with AFSTYLA; 3 now have titer values in the low titer range and 2 experienced successful eradication of the inhibitor.

No PTPs developed neutralizing antibodies (inhibitors) to Factor VIII or antibodies against chinese hamster ovary (CHO) host cell proteins at any time during the completed clinical studies. Four subjects in the adult/adolescent study and 10 subjects in the pediatric study were negative for non-neutralizing anti-drug antibodies (ADAs) at screening and turned

positive during the clinical study. Two of the adult/adolescent subjects and 3 of the pediatric subjects who developed ADAs were negative at end of study visit. No adverse events were associated with the development of ADAs. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, it may be misleading to compare the incidence of antibodies to AFSTYLA with the incidence of antibodies to other products.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with AFSTYLA use in pregnant women to inform on drug-associated risk. No developmental or animal reproduction toxicity studies were conducted with AFSTYLA. Thus, the risk of developmental toxicity including, structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, and alterations to growth is not known. In the US general population, the estimated background risk of major birth defects occurs in 2-4% of the general population and miscarriage occurs in 15-20% of clinically recognized pregnancies. AFSTYLA should be given to a pregnant woman only if clearly needed.

8.2 Lactation

Risk Summary

There is no information regarding the excretion of AFSTYLA in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AFSTYLA and any potential adverse effects on the breastfed infant from AFSTYLA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and efficacy studies with AFSTYLA have been performed in 98 previously treated pediatric patients <18 years of age. Fourteen adolescent subjects ≥12 to <18 years were enrolled in the adult/adolescent safety and efficacy study. Thirty-five subjects 0 to <6 years and 49 subjects ≥6 to <12 years were enrolled in a pediatric safety and efficacy study *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*. Because clearance (based on per kg body weight) has been shown to be higher in the pediatric population 0 to <12 years, more frequent or higher doses of AFSTYLA based on body weight may be needed *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use

Clinical studies of AFSTYLA did not include subjects over 65 years to determine whether or not they respond differently from younger subjects.

11 DESCRIPTION

AFSTYLA is a single-chain recombinant Factor VIII produced in chinese hamster ovary (CHO) cells. It is a construct where the B-domain occurring in wild type full-length Factor VIII has been truncated and 4 amino acids of the adjacent acidic a3 domain were removed (amino acids 765 to 1652 of full-length Factor VIII). AFSTYLA is expressed as a single-chain Factor VIII molecule with covalent linkage between heavy and light chains; thereby keeping the molecule in the single chain form resulting in increased stability and increased von Willebrand Factor (VWF) affinity. Except for a new N-glycosylation site at the junction between heavy and light chains, the post-translational modifications are comparable to endogenous Factor VIII.

AFSTYLA is purified by a controlled multi-step process including two virus reduction steps complementing each other in their mode of action. No human or animal derived proteins are used in the purification or formulation processes.

AFSTYLA is a preservative-free, sterile, non-pyrogenic, lyophilized powder to be reconstituted with sterile water for injection (sWFI) for intravenous injection. AFSTYLA is available in single-use vials containing the labeled amount of Factor VIII activity, expressed in IU. Each vial contains nominally 250, 500, 1000, 1500, 2000, 2500, or 3000 IU of AFSTYLA. The actual potency is labeled on each AFSTYLA vial and carton. After reconstitution of the lyophilized powder, all dosage strengths yield an almost colorless to slightly opalescent solution. The concentrations of excipients based on the vial size, as well as the amount of sWFI for reconstitution are provided in the table below.

Nominal Composition after Reconstitution with sWFI

Ingredient	250 IU vial	500 IU vial	1000 IU vial	1500 IU vial	2000 IU vial	2500 IU vial	3000 IU vial
rVIII-Single Chain	100 IU/mL	200 IU/mL	400 IU/mL	300 IU/mL	400 IU/mL	500 IU/mL	600 IU/mL
L-Histidine	3.1 mg/mL	3.1 mg/mL	3.1 mg/mL	3.1 mg/mL	3.1 mg/mL	3.1 mg/mL	3.1 mg/mL
Polysorbate 80	0.2 mg/mL	0.2 mg/mL	0.2 mg/mL	0.2 mg/mL	0.2 mg/mL	0.2 mg/mL	0.2 mg/mL
Calcium chloride	0.4 mg/mL	0.4 mg/mL	0.4 mg/mL	0.4 mg/mL	0.4 mg/mL	0.4 mg/mL	0.4 mg/mL
Sodium chloride	16.4 mg/mL	16.4 mg/mL	16.4 mg/mL	16.4 mg/mL	16.4 mg/mL	16.4 mg/mL	16.4 mg/mL
Sucrose	6 mg/mL	6 mg/mL	6 mg/mL	6 mg/mL	6 mg/mL	6 mg/mL	6 mg/mL
Water for Injection	2.5 mL	2.5 mL	2.5 mL	5 mL	5 mL	5 mL	5 mL

The number of units of Factor VIII administered is expressed in IU, which are related to the current WHO standard for Factor VIII products. One IU of Factor VIII activity in plasma is equivalent to that quantity of Factor VIII in 1 mL of normal plasma. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for Factor VIII in plasma).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

AFSTYLA is a recombinant protein that replaces the missing Coagulation Factor VIII needed for effective hemostasis. AFSTYLA is a single polypeptide chain with a truncated B-domain that allows for a covalent bridge to link the Factor VIII heavy and light chains. AFSTYLA has demonstrated a higher VWF affinity relative to full-length rFVIII.[1] VWF stabilizes Factor VIII and protects it from degradation. Activated AFSTYLA has an amino acid sequence identical to endogenous FVIIIa.

12.2 Pharmacodynamics

Hemophilia A is an X-linked hereditary disorder of blood coagulation due to decreased levels of Factor VIII and results in bleeding into joints, muscles or internal organs, either spontaneously or as result of accidental or surgical trauma. Replacement therapy increases the plasma levels of Factor VIII enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

12.3 Pharmacokinetics

Subjects ≥12 years

The pharmacokinetics (PK) of AFSTYLA were evaluated in 91 (81 adults ≥18 years and 10 adolescents ≥12 to <18 years) previously treated subjects following an intravenous injection of a single dose of 50 IU/kg.

The PK parameters (Table 5) were based on plasma Factor VIII activity measured by the chromogenic assay after the first dose (initial PK assessment). The PK profile obtained 3 to 6 months after the initial PK assessment was comparable with the PK profile obtained after the first dose.

Table 5. Pharmacokinetic Parameters (Arithmetic Mean, Coefficient of Variation [CV%]) in Adults and Adolescents Following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Assay

PK Parameters	≥18 years (N=81)	≥12 to <18 years (N=10)
IR (IU/dL)/(IU/kg)	2.00 (20.8)	1.69 (24.8)
C_{max} (IU/dL)	106 (18.1)	89.7 (24.8)
$AUC_{0\text{-}inf}$ (IU*h/dL)	1960 (33.1)	1540 (36.5)
$t_{1/2}$ (h)	14.2 (26.0)	14.3 (33.3)
MRT (h)	20.4 (25.8)	20.0 (32.2)
CL (mL/h/kg)	2.90 (34.4)	3.80 (46.9)
V_{ss} (mL/kg)	55.2 (20.8)	68.5 (29.9)

IR = incremental recovery recorded at 30 minutes after injection; C_{max} = observed maximum plasma concentration; $AUC_{0\text{-}inf}$ = area under the Factor VIII activity time curve extrapolated to infinity; $t_{1/2}$ = half-life; MRT = mean residence time; CL = body weight adjusted clearance; V_{ss} = body weight adjusted volume of distribution at steady-state.

Children <12 years

Pharmacokinetic parameters of AFSTYLA were evaluated in 39 previously treated children (0 to <12 years) in open-label, multicenter studies following a 50 IU/kg intravenous injection of AFSTYLA.

Table 6 summarizes the PK parameters calculated from the pediatric data. These parameters were estimated based on the plasma Factor VIII activity over time profile.

Table 6. Comparison of Pharmacokinetic Parameters in Children by Age Category (Arithmetic Mean, Coefficient of Variation [CV%]) Following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Assay

PK Parameters	0 to <6 years (N=20)	≥6 to <12 years (N=19)
IR (IU/dL)/(IU/kg)	1.60 (21.1)	1.66 (19.7)
C_{max} (IU/dL)	80.2 (20.6)	83.5 (19.5)
$AUC_{0\text{-}inf}$ (IU*h/dL)	1080 (31.0)	1170 (26.3)
$t_{1/2}$ (h)	10.4 (28.7)	10.2 (19.4)
MRT (h)	12.4 (25.0)	12.3 (16.8)
CL (mL/h/kg)	5.07 (29.6)	4.63 (29.5)
V_{ss} (mL/kg)	71.0 (11.8)	67.1 (22.3)

IR = incremental recovery recorded at 30 minutes after injection for subjects 12 to < 18 years and at 60 minutes after injection for subjects 1 to <12 years; C_{max} = observed maximum plasma concentration; AUC = area under the Factor VIII activity time curve extrapolated to infinity; $t_{1/2}$ = half-life; MRT = mean residence time; CL = body weight adjusted clearance; V_{ss} = body weight adjusted volume of distribution at steady-state.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies investigating the carcinogenic effects of AFSTYLA have not been conducted. In vitro and in vivo testing of AFSTYLA for mutagenicity or effects on fertility were not performed.

14 CLINICAL STUDIES

The safety and efficacy of AFSTYLA were evaluated in two studies: an Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study in adults/adolescents as well as in an Open-label Pharmacokinetic, Efficacy and Safety study in children. These studies characterized the PK of AFSTYLA and determined hemostatic efficacy in the control of bleeding events, the prevention of bleeding events in prophylaxis and in the adult/adolescent study determined hemostatic efficacy during perioperative management of bleeding in subjects undergoing surgical procedures.

The adult/adolescent study enrolled a total of 175 previously treated male subjects with severe hemophilia A (<1% endogenous Factor VIII activity). Subjects ranged in age from 12 to 65 years, including 14 adolescent subjects (≥12 to <18 years). Of the 175 enrolled subjects, 174 received at least one dose of AFSTYLA and 173 (99%) were evaluable for efficacy. A total of 161 subjects (92.5%) completed the study. A total of 120 (69.0%) subjects were treated for at least 50 EDs and 52 (29.9%) of those subjects were treated for at least 100 EDs. Subjects received a total of 14,592 injections with a median of 67.0 (range 1 to 395) injections per subject.

The pediatric study enrolled 84 previously treated male subjects with severe hemophilia A (35 subjects 0 to <6 years and 49 subjects ≥6 to <12 years). Of the 84 enrolled subjects, all received at least one dose of AFSTYLA and 83 (99%) were evaluable for efficacy. A total of 65 (77.4%) subjects were treated for at least 50 EDs and 8 (9.5%) of those subjects were treated for at least 100 EDs. Subjects received a total of 5,313 injections with a median of 59 (range 4 to 145) injections per subject.

On-demand Treatment and Control of Bleeding Episodes

In the adult/adolescent study a total of 848 bleeding episodes were treated with AFSTYLA and 835 received an efficacy assessment by the investigator. The majority of the bleeding episodes occurred in joints. The median dose per injection used to treat a bleeding episode was 31.7 IU/kg (range 6 to 84 IU/kg). Of the 848 bleeding episodes, 686 (81%) were controlled with a single AFSTYLA injection and another 107 (13%) were controlled with 2 injections. Fifty-five (6%) of the 848 bleeding episodes required 3 or more injections. For 94% of bleeding episodes the hemostatic efficacy rating by the investigator was either excellent or good.

In the pediatric study a total of 347 bleeding episodes were treated with AFSTYLA all of which received an efficacy assessment by the investigator. The majority of the bleeding episodes occurred in joints. The median dose per injection used to treat a bleeding episode was 27.3 IU/kg (range 16 to 76 IU/kg). Of the 347 bleeding episodes, 298 (86%) were controlled with a single AFSTYLA injection and another 34 (10%) were controlled with 2 injections. Fifteen (4%) of the 347 bleeding episodes required 3 or more injections. For 96% of bleeding episodes the hemostatic efficacy rating by the investigator was either excellent or good.

Assessment of response to treatment of bleeds by the investigator was as follows:

Excellent: Pain relief and/or improvement in signs of bleeding (i.e., swelling, tenderness, and/or increased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 hours after the first infusion

Good: Pain relief and/or improvement in signs of bleeding at approximately 8 hours after the first infusion, but requires two infusions for complete resolution

Moderate: Probable or slight beneficial effect within approximately 8 hours after the first infusion; requires more than two infusions for complete resolution

No response: No improvement at all or condition worsens (i.e., signs of bleeding) after the first infusion and additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Efficacy in control of bleeding episodes in both studies is summarized in Table 7.

Table 7. Efficacy of AFSTYLA in Control of Bleeding

Bleeding Episodes Treated	Adult and Adolescent (≥12 to 65 years of age) (N=848)	Pediatric (0 to <12 years of age) (N=347)
Number of injections		
1 injection, n (%)	686 (81%)	298 (85.9%)
2 injections, n (%)	107 (13%)	34 (9.8%)
3 injections, n (%)	29 (3%)	8 (2.3%)
>3 injections, n (%)	26 (3%)	7 (2.0%)
Efficacy evaluation by investigator	**(N=835)**	**(N=347)**
Excellent or Good, n (%)	783 (94%)	334 (96.3%)
Moderate, n (%)	52 (6%)	12 (3.5%)
No response, n (%)	0	1 (0.3%)

Routine Prophylaxis

Adult and Adolescent Study

In the adult/adolescent and pediatric studies, subjects received prophylaxis in a regimen that was determined by the investigator, taking into account the subject's Factor VIII treatment regimen used prior to enrollment and the subject's bleeding phenotype.

In the adult/adolescent study, 54% of the 146 subjects on prophylaxis received AFSTYLA 3 times weekly; 32% of subjects received AFSTYLA 2 times weekly; 6% received AFSTYLA every other day, and 8% of subjects received other regimens.

The annualized bleeding rate (ABR) was comparable between subjects on a 3 times weekly regimen (median ABR of 1.53) and those on a 2 times weekly regimen (median ABR of 0.00). The annualized spontaneous bleeding rate (AsBR) was also comparable between subjects on a 3 times weekly regimen (median AsBR of 0.0) and those on a 2 times weekly regimen (median AsBR of 0.0). The number of subjects who needed dose adjustments was comparable between the two groups (34.2% [27 subjects] for three times weekly and 27.7% [13 subjects] for twice weekly).

The median prescribed dose for subjects on a 3 times weekly prophylaxis regimen was 30 IU/kg (12 to 50 IU/kg). The median prescribed dose for subjects on a 2 times weekly regimen was 35 IU/kg (17 to 50 IU/kg).

The ABR in prophylaxis (median of 1.14) was significantly lower ($p < 0.0001$) than the ABR that was observed in subjects treated on-demand (median of 19.64). Sixty-three of 146 subjects (43%) experienced no bleeding episodes while on prophylaxis. There were no severe or life-threatening bleeds (e.g., intracranial hemorrhage) in subjects receiving prophylaxis.

Pediatric Study

In the pediatric study, 54% of the 80 subjects on prophylaxis received AFSTYLA 2 times a week; 30% of subjects received AFSTYLA 3 times a week; 4% received AFSTYLA every other day, and 12% of subjects received other regimens.

Twenty-one of 80 subjects (26%) experienced no bleeding episodes while on prophylaxis. There was one severe bleed (hip joint hemorrhage) in the pediatric study that was successfully treated.

For subjects on prophylaxis the overall ABR was 3.69, with a median ABR of 2.30 for subjects on a 3 times a week regimen and 4.37 for subjects on a 2 times a week regimen. The median AsBR (0.00) was identical between subjects on the 3 times a week and 2 times a week regimens.

The median prescribed dose for subjects on a 3 times a week regimen was 32 IU/kg (19 to 50 IU/kg) and for subjects on a 2 times a week regimen was 35 IU/kg (20 to 57 IU/kg).

The ABRs for prophylaxis and on-demand in both studies are summarized in Table 8.

Table 8. Summary of Annualized Bleeding Rate (ABR) by AFSTYLA Treatment Regimen

	Phase I/III Adult/ Adolescent Study		Phase III Pediatric Study	
	Prophylaxis (N=146)	On-demand (N=27)	Prophylaxis (N=80)	On-demand (N=3)
Overall ABR Median (IQR*)	1.14 (0–4.2)	19.64 (6.2–46.5)	3.69 (0–7.2)	78.56 (35.1–86.6)
Annualized Spontaneous Bleeding Rate (AsBR) Median (IQR*)	0 (0–2.4)	11.73 (2.8–36.5)	0 (0–2.2)	31.76 (0–42.7)
Number of subjects with zero bleeding episodes	63 (43.2%)	1 (3.7%)	21 (26.3%)	0

* IQR = interquartile range, 25th percentile to 75th percentile

Perioperative Management of Bleeding

Thirteen subjects in the adult/adolescent study underwent a total of 16 surgical procedures. Overall, investigators assessed hemostatic efficacy of AFSTYLA in perioperative management of bleeding as excellent in 15 of 16 surgeries and as good in 1 of 16 surgeries (see Table 9). Median factor consumption pre- and intra-operatively was 89.4 IU/kg (range 40.5 to 108.6 IU/kg).

Assessment of hemostasis during surgical procedures by the investigator was as follows:

Excellent: Hemostasis clinically not significantly different from normal (e.g., achieved hemostasis comparable to that expected during similar surgery in a non-factor deficient patient) in the absence of other hemostatic intervention and estimated blood loss during surgery is not more than 20% higher than the predicted blood loss for the intended surgery

Good: Normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient in the absence of other hemostatic intervention) or estimated blood loss is >20%, but ≤30% higher than the predicted blood loss for intended surgery

Moderate: Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate hemorrhage that is difficult to control) with estimated blood loss greater than what is defined as good

Poor/No Response: Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that is difficult to control) and/or additional hemostatic intervention required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Table 9. Efficacy of AFSTYLA in Perioperative Management of Bleeding

Procedure	Efficacy Evaluation	Factor Consumption (IU/kg) (pre- and intra-operatively)
Extraction of wisdom teeth	Excellent	51.09
Abdominal hernia repair	Excellent	47.89
Elbow replacement	Excellent	108.58
Ankle arthroplasty	Excellent	76.83
Knee replacement (5)	Excellent (4), Good (1)	92.49 100.9 67.26 105.79 86.09
Cholecystectomy and Lengthening of the Achilles tendon combined with: Straightening of the right toes	Excellent Excellent	105.95
Circumcision (3)	Excellent (3)	99.04 92.74 81.5
Open reduction internal fixation (ORIF) right ankle	Excellent	89.36
Hardware removal, Right ankle	Excellent	40.45

15 REFERENCES

[1] Zollner S, Raquet E, Claar Ph, Müller-Cohrs J, Metzner HJ, Weimer Th, Pragst I, Dickneite G, Schulte S. Non-clinical pharmacokinetics and pharmacodynamics of rVIII-SingleChain, a novel recombinant single-chain factor VIII, Thrombosis Research 2014; 134: 125-131.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

AFSTYLA is supplied in a kit containing a lyophilized powder in a single-use vial labeled with the amount of Factor VIII activity, expressed in international units (IU). Actual Factor VIII activity in International Units (IU) is stated on the AFSTYLA carton and vial label.

AFSTYLA is packaged with Sterile Water for Injection, USP (2.5 mL for reconstitution of 250, 500 or 1000 IU or 5 mL for reconstitution of 1500, 2000, 2500, or 3000 IU AFSTYLA), one Mix2Vial filter transfer set, and one sterile alcohol swab. Components are not made of natural rubber latex.

Nominal Strength	Fill Size Color Indicator	Kit NDC
250 IU	Orange	69911-474-02
500 IU	Blue	69911-475-02
1000 IU	Green	69911-476-02
1500 IU	Turquoise	69911-480-02
2000 IU	Purple	69911-477-02
2500 IU	Cool Grey	69911-481-02
3000 IU	Yellow	69911-478-02

Storage and Handling

- Store AFSTYLA in the original package to protect the AFSTYLA vials from light.
- Store AFSTYLA in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the diluent vial. AFSTYLA can be stored at room temperature, not to exceed 25°C (77°F), for a single period of up to 3 months, within the expiration date printed on the carton and vial labels.
- Record the starting date of room temperature on the unopened product carton. Once stored at room temperature, do not return the product to the refrigerator. The shelf-life then expires after storage at room temperature for 3 months, or after the expiration date on the product vial, whichever is earlier.
- Do not use AFSTYLA after the expiration date indicated on the vial.
- The reconstituted product (after mixing dry product with diluent) can be stored at 2°C to 8°C (36°F to 46°F), or at room temperature, not to exceed 25°C (77°F), for up to 4 hours.
- Protect from direct sunlight.
- After reconstitution, if the product is not used within 4 hours, it must be discarded.
- Do not use AFSTYLA if the reconstituted solution is cloudy or has particulate matter.
- Discard any unused AFSTYLA.

17 PATIENT COUNSELING INFORMATION

Advise patients to:

- Read the FDA-approved Patient Labeling (Patient Product Information and Instructions for Use).
- Discontinue use of AFSTYLA in case of a hypersensitivity reaction and contact their healthcare provider and/or seek emergency care, depending on the severity of the reaction. Early signs of hypersensitivity reactions may include hives, itching, facial swelling, tightness of the chest, and wheezing *[see Warnings and Precautions (5.1)]*.
- Contact their healthcare provider or hemophilia treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII replacement therapy, as in some cases this may be a manifestation of an inhibitor *[see Warnings and Precautions (5.2)]*.
- Report any adverse reactions or problems following AFSTYLA administration to their healthcare provider.

Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
for:
CSL Behring Recombinant Facility AG
Bern 22, Switzerland 3000
US License No. 2009

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

FDA-Approved Patient Labeling

Patient Product Information (PPI)

AFSTYLA / af stŷ lah /

Antihemophilic Factor (Recombinant), Single Chain

Freeze-Dried Powder for Reconstitution

This leaflet summarizes important information about AFSTYLA. Please read it carefully before using AFSTYLA. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about AFSTYLA. If you have any questions after reading this, ask your healthcare provider.

What is the most important information I need to know about AFSTYLA?

- **Your healthcare provider or hemophilia treatment center will instruct you on how to do an infusion on your own.**
- Carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing this medicine.

What is AFSTYLA?

- AFSTYLA, Antihemophilic Factor (Recombinant), Single Chain is a medicine used to replace clotting Factor VIII that is missing in patients with hemophilia A.
- Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.
- Does not contain human plasma-derived proteins or albumin.
- Your healthcare provider may give you this medicine when you have surgery.
- Is used to treat and control bleeding in all patients with hemophilia A.
- Can reduce the number of bleeding episodes when used regularly (prophylaxis) and reduce the risk of joint damage due to bleeding.
- Is not used to treat von Willebrand disease.

Who should not use AFSTYLA?

You should not use AFSTYLA if you:

- Have had a life-threatening allergic reaction to it in the past.
- Are allergic to its ingredients or hamster proteins.

Tell your healthcare provider if you are pregnant or breastfeeding because AFSTYLA may not be right for you.

What should I tell my healthcare provider before using AFSTYLA?

Tell your healthcare provider if you:

- Have or have had any medical problems.
- Take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies.
- Have any allergies, including allergies to hamster proteins.
- Are pregnant or planning to become pregnant. It is not known if AFSTYLA may harm your unborn baby.
- Are breastfeeding. It is not known if AFSTYLA passes into the milk or if it can harm your baby.
- Have been told you have inhibitors to Factor VIII (because this medicine may not work for you).

How should I use AFSTYLA?

- Administered directly into the bloodstream.
- Use as ordered by your healthcare provider.
- You should be trained on how to do intravenous injections by your healthcare provider or hemophilia treatment center. Once trained, many patients with hemophilia A are able to inject this medicine by themselves or with the help of a family member.
- Your healthcare provider will tell you how much to use based on your weight, the severity of your hemophilia A, and where you are bleeding.
- You may need to have blood tests done after getting to be sure that your blood level of Factor VIII is high enough to clot your blood.
- Call your healthcare provider right away if your bleeding does not stop after taking this medicine.

What are the possible side effects of AFSTYLA?

- Allergic reactions may occur. Immediately stop treatment and call your healthcare provider right away if you get a rash or hives, itching, tightness of the chest or throat, difficulty breathing, light-headedness, dizziness, nausea, or decrease in blood pressure.
- Your body may form inhibitors to Factor VIII. An inhibitor is a part of the body's defense system. If you form inhibitors, it may stop this medicine from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.
- Common side effects are dizziness and allergic reactions.
- These are not the only side effects possible. Tell your healthcare provider about any side effect that bothers you or does not go away.

What are the AFSTYLA dosage strengths?

AFSTYLA comes in 5 different dosage strengths: 250, 500, 1000, 1500, 2000, 2500 or 3000 International Units (IU). The actual strength is printed on the carton and vial label.

Fill Size Color Indicator	Strengths
Orange	Dosage strength of approximately 250 IU per vial
Blue	Dosage strength of approximately 500 IU per vial
Green	Dosage strength of approximately 1000 IU per vial
Turquoise	Dosage strength of approximately 1500 IU per vial
Purple	Dosage strength of approximately 2000 IU per vial
Cool Grey	Dosage strength of approximately 2500 IU per vial
Yellow	Dosage strength of approximately 3000 IU per vial

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider.

How should I store AFSTYLA?

- Store this medicine in the original package to protect the vials from light.
- Store this medicine in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the diluent vial. It can be stored at room temperature, not to exceed 25°C (77°F), for a single period of up to 3 months, within the expiration date printed on the carton and vial labels.
- If stored at room temperature, record the date that this medicine is removed from refrigeration on the top flap of the carton in the area provided. After storage at room temperature, do not return the product to the refrigerator. The powder form for the product then expires after storage at room temperature for 3 months, or after the expiration date on the product vial, whichever is earlier.
- The reconstituted product (after mixing dry product with diluent) can be stored for 4 hours at a temperature not to exceed 25°C (77°F). Protect from direct sunlight. After reconstitution, if the product is not used within 4 hours, it must be discarded.

What else should I know about AFSTYLA?

- Medicines are sometimes prescribed for purposes other than those listed here. Do not use this medicine for a condition for which it is not prescribed. Do not share with other people, even if they have the same symptoms that you have.

Instructions for Use of AFSTYLA

For intravenous use after reconstitution only

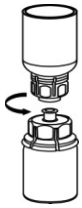
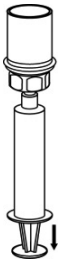
This medicine is infused into a vein. Your healthcare provider or hemophilia treatment center should teach you how to do infusions on your own.

Always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using AFSTYLA. If you are unsure of the instructions, call your healthcare provider before using AFSTYLA. Call your healthcare provider right away if bleeding is not controlled after using AFSTYLA. Your healthcare provider will prescribe the dose that you should take. You may need to take blood tests from time to time. Talk to your healthcare provider before traveling. Dispose of all unused solution, empty vial(s), and other used medical supplies in an appropriate medical waste container.

- **Always work on a clean flat surface** and wash your hands before performing the reconstitution procedures.
- Use only the components for reconstitution that are provided with each package.
- If a package is opened or damaged, do not use and contact your healthcare provider.
- Do not use AFSTYLA beyond the expiration date on the vial and carton labels. If stored at room temperature, the dry product (prior to reconstitution) expires after storage at room temperature for 3 months or after the expiration date on the product vial, whichever is earlier.
- Look at the mixed (reconstituted) solution. Do not use AFSTYLA if the reconstituted solution is cloudy, contains any particles, or is discolored.
- AFSTYLA is for single use only and contains no preservatives. Discard partially used vials.

AFSTYLA Reconstitution Instructions

1.	Ensure that the AFSTYLA vial and diluent vial are at room temperature.	
2.	Place the AFSTYLA vial, diluent vial, and Mix2Vial® transfer set on a flat surface.	
3.	Remove AFSTYLA and diluent vial flip caps. Wipe the stoppers with the sterile alcohol swab provided and allow the stoppers to dry prior to opening the Mix2Vial transfer set package.	
4.	Open the Mix2Vial transfer set package by peeling away the lid (Fig. 1). Leave the Mix2Vial transfer set in the clear package.	 Fig. 1
5.	Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Fig. 2).	 Fig. 2
6.	Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, not the Mix2Vial transfer set (Fig. 3).	 Fig. 3
7.	With the AFSTYLA vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the AFSTYLA vial (Fig. 4). The diluent will automatically transfer into the AFSTYLA vial.	 Fig. 4
8.	With the diluent and AFSTYLA vial still attached to the Mix2Vial transfer set, gently swirl the AFSTYLA vial to ensure that the AFSTYLA is fully dissolved (Fig. 5). Do not shake the vial.	 Fig. 5

9.	With one hand, grasp the AFSTYLA side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set, and unscrew the set into two pieces. (Fig. 6).	 Fig. 6
10.	Draw air into an empty, sterile syringe. While the AFSTYLA vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the AFSTYLA vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly. (Fig. 7).	 Fig. 7
11.	Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Fig. 8).	 Fig. 8
12.	After reconstitution, infuse immediately or within 4 hours. The mixed (reconstituted) solution may be stored at room temperature, not to exceed 25°C (77°F), for up to 4 hours. Do not freeze. Protect from direct sunlight.	
13.	Record treatment - Remove the peel-off portion of the label from each vial used, and affix it to the patient's treatment diary/log book or scan the vial if recording the infusion electronically.	
14.	If the dose requires more than one vial, use a separate unused Mix2Vial transfer set for each product vial. Repeat step 10 to pool the contents into one syringe.	

Administration (intravenous injection)

- Do not mix AFSTYLA in the same tubing or container with other medicinal products.
- Attach the syringe containing the mixed (reconstituted) solution to a sterile infusion set and give an injection as directed by your healthcare provider or hemophilia treatment center.
- Administer intravenously. Do not exceed infusion rate of 10 mL per minute.

Resources at CSL Behring available to the patient:
For Adverse Reaction Reporting contact:
CSL Behring Pharmacovigilance Department at 1-866-915-6958

Contact CSL Behring to receive more product information:
Customer Support 1-800-683-1288

For more information, visit www.AFSTYLA.com

Manufactured by:
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for:
CSL Behring Recombinant Facility AG
Bern 22, Switzerland 3000
US License No. 2009

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HUMATE-P safely and effectively. See full prescribing information for HUMATE-P.

HUMATE-P®
[Antihemophilic Factor/von Willebrand Factor Complex (Human)]
Lyophilized Powder for Reconstitution for Intravenous Use Only.
Initial U.S. Approval: 1986

---------- INDICATIONS AND USAGE ----------

Humate-P is an Antihemophilic Factor/von Willebrand Factor (VWF) Complex (Human) indicated for:

- Hemophilia A – Treatment and prevention of bleeding in adults (1.1).
- Von Willebrand disease (VWD) – in adults and pediatric patients in the (1) Treatment of spontaneous and trauma-induced bleeding episodes, and (2) Prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where the use of desmospressin is known or suspected to be inadequate (1.2). Humate-P is not indicated for the prophylaxis of spontaneous bleeding episodes in VWD.

---------- DOSAGE AND ADMINISTRATION ----------

For intravenous use only.

Hemophilia A

- One International Unit (IU) of factor VIII (FVIII) activity per kg body weight increases the circulating FVIII level by approximately 2.0 IU/dL. Individualize dosage based on the patient's weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors (2.1).

VWD

- Treatment of bleeding episodes – 40-80 IU VWF:Ristocetin Cofactor (RCo) per kg body weight (BW) every 8-12 hours (2.2).
- Prevention of excessive bleeding during and after surgery for all types of VWD (2.3).

Type of Surgery (see Table 3 for complete surgical dosing)	Calculation of Loading Dose Initial maintenance dose should be half the loading dose (see Table 4 for monitoring recommendations).
Major Surgery (2.3)	$\frac{\Delta^* \text{ VWF:RCo x BW (kg)}}{\text{IVR}^\dagger}$ = IU VWF:RCo required
Minor/Oral Surgery‡ (2.3)	$\frac{\Delta^* \text{ VWF:RCo x BW (kg)}}{\text{IVR}}$ = IU VWF:RCo required
Emergency Surgery (2.3)	Administer a dose of 50-60 IU VWF:RCo/kg BW

* Δ = Target peak plasma VWF:RCo level – baseline plasma VWF:RCo level.
† IVR = *in vivo* recovery as measured in the patient. If the IVR is unknown, use 2.0 IU/dL per IU/kg.
‡ Oral surgery is defined as extraction of fewer than three teeth, if the teeth are non-molars and have no bony involvement.

---------- DOSAGE FORMS AND STRENGTHS ----------

Humate-P is available as a lyophilized powder in single-use vials that contain the labeled amount of VWF:RCo and FVIII activity expressed in IU. The average ratio of VWF:RCo to FVIII is 2.4:1. Approximate potencies are shown below (3):

VWF:RCo/vial	FVIII/vial	Diluent
600 IU	250 IU	5 mL
1200 IU	500 IU	10 mL
2400 IU	1000 IU	15 mL

---------- CONTRAINDICATIONS ----------

- Anaphylactic or severe systemic reaction to antihemophilic factor or VWF preparations (4).

---------- WARNINGS AND PRECAUTIONS ----------

- VWD patients receiving Humate-P may be at risk of developing thromboembolic events (5.1).
- Monitor for intravascular hemolysis and decreasing hematocrit values in patients with A, B, and AB blood groups who are receiving large or frequent doses (5.2).
- Monitor VWF:RCo and FVIII levels in VWD patients, especially those undergoing surgery (5.3).
- Products made from human plasma may contain infectious agents (e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent) (5.4).

---------- ADVERSE REACTIONS ----------

- Most common adverse reactions observed by >5% of subjects after receiving Humate-P are allergic-anaphylactic reactions (e.g., urticaria, chest tightness, rash, pruritus, edema) and, in patients undergoing surgery, postoperative wound and injection-site bleeding, and epistaxis (6).

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).
- The hemostatic efficacy of Humate-P has been studied in 34 pediatric subjects with VWD (8.4). Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo (12.3).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: September 2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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CSL Behring

FULL PRESCRIBING INFORMATION

Humate-P®
Antihemophilic Factor/von Willebrand Factor Complex (Human)

1 INDICATIONS AND USAGE

1.1 Hemophilia A

Humate-P, Antihemophilic Factor/von Willebrand Factor Complex (Human), is indicated for treatment and prevention of bleeding in adults with hemophilia A (classical hemophilia).

1.2 Von Willebrand Disease (VWD)

Humate-P is also indicated in adult and pediatric patients with von Willebrand disease (VWD) for:
(1) treatment of spontaneous and trauma-induced bleeding episodes, and

(2) prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where use of desmopressin (DDAVP) is known or suspected to be inadequate.

Controlled clinical trials to evaluate the safety and efficacy of prophylactic dosing with Humate-P to prevent spontaneous bleeding have not been conducted in VWD subjects *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Therapy for Hemophilia A

One International Unit (IU) of Factor VIII (FVIII) activity per kg body weight will increase the circulating FVIII level by approximately 2.0 International Units (IU)/dL. Dosage must be individualized based on the patient's weight, type and severity of hemorrhage, FVIII level, and presence of inhibitors. Judge the adequacy of treatment by clinical effects and, in all cases, adjust doses as needed based on clinical judgment and on frequent monitoring of the patient's FVIII level. Table 1 provides dosing recommendations for the treatment of hemophilia A in adults.

Table 1. Dosing Recommendations for the Treatment of Hemophilia A in Adults[1]

Hemorrhagic Event	Dosage (IU FVIII:C/kg Body Weight)
Minor hemorrhage: • Early joint or muscle bleed • Severe epistaxis	Loading dose 15 IU FVIII:C/kg to achieve a FVIII:C plasma level of approximately 30% of normal; one infusion may be sufficient. If needed, half of the loading dose may be given once or twice daily for 1-2 days.
Moderate hemorrhage: • Advanced joint or muscle bleed • Neck, tongue, or pharyngeal hematoma (without airway compromise) • Tooth extraction • Severe abdominal pain	Loading dose 25 IU FVIII:C/kg to achieve a FVIII:C plasma level of approximately 50% of normal, followed by 15 IU FVIII:C/kg every 8-12 hours for the first 1-2 days to maintain the FVIII:C plasma level at 30% of normal. Continue the same dose once or twice daily for up to 7 days or until adequate wound healing is achieved.
Life-threatening hemorrhage: • Major surgery • Gastrointestinal bleeding • Neck, tongue, or pharyngeal hematoma (with potential for airway compromise) • Intracranial, intraabdominal, or intrathoracic bleeding • Fractures	Initially 40-50 IU FVIII:C/kg, followed by 20-25 IU FVIII:C/kg every 8 hours to maintain the FVIII:C plasma level at 80-100% of normal for 7 days. Continue the same dose once or twice daily for another 7 days to maintain the FVIII:C level at 30-50% of normal.

IU = International Units.

2.2 Treatment of Bleeding Episodes in VWD

Administer 40 to 80 International Units (IU) VWF:RCo (corresponding to 17 to 33 International Units (IU) FVIII in Humate-P) per kg body weight every 8 to 12 hours. Adjust the dosage based on the extent and location of bleeding. Administer repeat doses as long as needed based on monitoring of appropriate clinical and laboratory measures [*see Warnings and Precautions (5.2, 5.3)*]. Expected levels of VWF:RCo are based on an expected *in vivo* recovery (IVR) of 2.0 International Units (IU)/dL rise per International Unit (IU)/kg VWF:RCo administered. The administration of 1 IU of FVIII per kg body weight can be expected to lead to a rise in circulating VWF:RCo of approximately 5 International Units (IU)/dL. Table 2 provides dosing recommendations for adult and pediatric patients [*see Use in Specific Populations (8.4)*].[2]

Table 2. VWF:RCo Dosing Recommendations for the Treatment of Bleeding Episodes by VWD Type

VWD Type	Severity of Hemorrhage	Dosage (IU* VWF:RCo/kg Body Weight)
Type 1 VWD – Mild (baseline VWF:RCo activity typically >30%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia)	Typically treatable with desmopressin.
	Minor (when desmopressin is known or suspected to be inadequate) Major† (e.g., severe or refractory epistaxis, GI bleeding, CNS trauma, traumatic hemorrhage)	Loading dose 40-60 IU/kg. Then 40-50 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-50 IU/kg daily for up to 7 days.
Type 1 VWD – Moderate or severe (baseline VWF:RCo typically <30%)	Minor (e.g., epistaxis, oral bleeding, menorrhagia)	40-50 IU/kg (1 or 2 doses).
	Major (e.g., severe or refractory epistaxis, GI bleeding, CNS trauma, hemarthrosis, traumatic hemorrhage)	Loading dose 50-75 IU/kg. Then 40-60 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-60 IU/kg daily for up to 7 days.
Type 2 VWD (all variants) and Type 3 VWD	Minor (clinical indications above)	40-50 IU/kg (1 or 2 doses).
	Major (clinical indications above)	Loading dose 60-80 IU/kg. Then 40-60 IU/kg every 8-12 hours for 3 days to keep the trough level of VWF:RCo >50%. Then 40-60 IU/kg daily for up to 7 days.

* IU = International Units.

† For major bleeds in all types of VWD where repeated dosing is required, monitor and maintain the patient's FVIII level according to the guidelines for hemophilia A therapy.

2.3 Prevention of Excessive Bleeding During and After Surgery in VWD

The following information provides guidelines for calculating loading and maintenance doses of Humate-P for patients undergoing surgery. However **in the case of emergency surgery**, administer a loading dose of 50 to 60 International Units (IU) VWF:RCo/kg body weight and, subsequently, closely monitor the patient's trough coagulation factor levels.

Measure incremental IVR and assess plasma VWF:RCo and FVIII:C levels in all patients prior to surgery when possible.

To determine IVR:
1. Measure the baseline plasma VWF:RCo level.
2. Infuse a calculated dose [International Units (IU)/kg] of VWF:RCo product intravenously at "time 0".
3. At "time+30 minutes", measure the plasma VWF:RCo level.

Use the following formula to calculate IVR:

$$\text{IVR} = \frac{(\text{Plasma VWF:RCo}_{\text{time+30 min}} - \text{Plasma VWF:RCo}_{\text{baseline}})\ \text{International Units (IU)/dL}}{\text{Calculated dose (International Units (IU)/kg)}}$$

For example, assuming a baseline VWF:RCo of 30 International Units (IU)/dL at "time 0", a calculated dose of 60 International Units (IU)/kg, and a VWF:RCo of 120 International Units (IU)/dL at "time+30 minutes", the IVR would be 1.5 International Units (IU)/dL per International Units (IU)/kg of VWF:RCo administered.

Loading Dose

Table 3 provides guidelines for calculating the loading dose for adult and pediatric patients based on the target peak plasma VWF:RCo level, the baseline VWF:RCo level, body weight in kilograms, and IVR. When individual recovery values are not available, a standardized loading dose can be used based on an assumed VWF:RCo IVR of 2.0 International Units (IU)/dL per International Unit (IU)/kg of VWF:RCo administered.

Table 3. VWF:RCo and FVIII:C Loading Dose Calculations for the Prevention of Excessive Bleeding During and After Surgery for All Types of VWD

Type of Surgery	VWF:RCo Target Peak Plasma Level	FVIII:C Target Peak Plasma Level	Calculation of Loading Dose (to be administered 1 to 2 hours before surgery)
Major	100 IU/dL	80-100 IU/dL	Δ^{*} VWF:RCo x $\frac{\text{BW (kg)}}{\text{IVR}^{\dagger}}$ = IU VWF:RCo required If the IVR is not available, assume an IVR of 2.0 IU/dL per IU/kg and calculate the loading dose as follows: (100 – baseline plasma VWF:RCo) x BW (kg)/2.0
Minor/Oral‡	50-60 IU/dL	40-50 IU/dL	Δ^{*} VWF:RCo x $\frac{\text{BW (kg)}}{\text{IVR}}$ = IU VWF:RCo required
Emergency	100 IU/dL	80-100 IU/dL	Administer a dose of 50-60 IU VWF:RCo/kg body weight.

IU = International Units.
BW = body weight.
* Δ = Target peak plasma VWF:RCo level – baseline plasma VWF:RCo level.
† IVR = *in vivo* recovery as measured in the patient.
‡ Oral surgery is defined as extraction of fewer than three teeth, if the teeth are non-molars and have no bony involvement. Extraction of more than one impacted wisdom tooth is considered major surgery due to the expected difficulty of the surgery and the expected blood loss, particularly in subjects with type 2A or type 3 VWD. Extraction of more than two teeth is considered major surgery in all patients.

For example, the loading dose of Humate-P required assuming a target VWF:RCo level of 100 International Units (IU)/dL, a baseline VWF:RCo level of 20 International Units (IU)/dL, an IVR of 2.0 International Units (IU)/dL per International Units (IU)/kg, and a body weight of 70 kg would be 2,800 International Units (IU) VWF:RCo, calculated as follows:

$$\frac{(100 \text{ IU/dL} - 20 \text{ IU/dL}) \times 70 \text{ kg}}{2.0 \text{ (IU/dL)/(IU/kg)}} = 2{,}800 \text{ IU VWF:RCo required}$$

IU = International Units.

Attaining a target peak FVIII:C plasma level of 80 to 100 International Units (IU) FVIII:C/dL for major surgery and 40 to 50 International Units (IU) FVIII:C/dL for minor surgery or oral surgery might require additional dosing with Humate-P. Because the ratio of VWF:RCo to FVIII:C activity in Humate-P is 2.4:1, any additional dosing will increase VWF:RCo proportionally more than FVIII:C. Assuming an incremental IVR of 2.0 International Units (IU) VWF:RCo/dL per International Units (IU)/kg infused, additional dosing to increase FVIII:C in plasma will also increase plasma VWF:RCo by approximately 5 International Units (IU)/dL for each International Unit (IU)/kg of FVIII administered.

Maintenance Doses

The initial maintenance dose of Humate-P for the prevention of excessive bleeding during and after surgery should be half of the loading dose, irrespective of additional dosing required to meet FVIII:C targets. Subsequent maintenance doses should be based on the patient's VWF:RCo and FVIII levels. Table 4 provides recommendations for target trough plasma levels (based on type of surgery and number of days following surgery) and minimum duration of treatment for subsequent maintenance doses. These recommendations apply to both adult and pediatric patients.

Table 4. VWF:RCo and FVIII:C Target Trough Plasma Level and Minimum Duration of Treatment Recommendations for Subsequent Maintenance Doses for the Prevention of Excessive Bleeding During and After Surgery

Type of Surgery	VWF:RCo Target Trough Plasma Level*		FVIII:C Target Trough Plasma Level*		Minimum Duration of Treatment
	Up to 3 days following surgery	After Day 3	Up to 3 days following surgery	After Day 3	
Major	>50 IU/dL	>30 IU/dL	>50 IU/dL	>30 IU/dL	72 hours
Minor	≥30 IU/dL	–	–	>30 IU/dL	48 hours
Oral†	≥30 IU/dL	–	–	>30 IU/dL	8-12 hours‡

IU = International Units.
* Trough levels for either coagulation factor should not exceed 100 IU/dL.
† Oral surgery is defined as extraction of fewer than three teeth, if the teeth are non-molars and have no bony involvement. Extraction of more than one impacted wisdom tooth is considered major surgery due to the expected difficulty of the surgery and the expected blood loss, particularly in subjects with type 2A or type 3 VWD. Extraction of more than two teeth is considered major surgery in all patients.
‡ Administer at least one maintenance dose following oral surgery based on individual pharmacokinetic values. Subsequent therapy with an antifibrinolytic agent is usually administered until adequate healing is achieved.

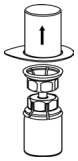
Based on individual pharmacokinetic-derived half-lives, the frequency of maintenance doses is generally every 8 or 12 hours; patients with shorter half-lives may require dosing every 6 hours. In the absence of pharmacokinetic data, it is recommended that Humate-P be administered initially every 8 hours with further adjustments determined by monitoring trough coagulation factor levels. When hemostatic levels are judged insufficient or trough levels are outside the recommended range, consider modifying the administration interval and/or the dose.

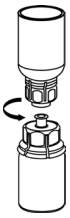
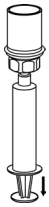
It is advisable to monitor trough VWF:RCo and FVIII:C levels at least once a day in order to adjust Humate-P dosing as needed to avoid excessive accumulation of coagulation factors. The duration of treatment generally depends on the type of surgery performed, but must be assessed for individual patients based on their hemostatic response [*see Clinical Studies (14.2)*].

2.4 Reconstitution and Administration

Humate-P is for intravenous use only.

- Prepare and administer using aseptic techniques.
- Use either the Mix2Vial® filter transfer set provided with Humate-P [*see How Supplied/Storage and Handling (16)*] or a commercially available double-ended needle and vented filter spike.
- Use plastic disposable syringes with Humate-P. Protein solutions of this type tend to adhere to the ground glass surface of all-glass syringes.
- Reconstitute Humate-P at room temperature as follows:

1. Ensure that the Humate-P vial and diluent vial are at room temperature.	
2. Place the Humate-P vial, diluent vial and Mix2Vial transfer set on a flat surface.	
3. Remove the Humate-P and diluent vial flip caps. Wipe the stoppers with an alcohol swab and allow the stoppers to dry prior to opening the Mix2Vial transfer set package.	
4. Open the Mix2Vial transfer set package by peeling away the lid (Figure 1). Leave the Mix2Vial transfer set in the clear package.	 Figure 1
5. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and push the plastic spike at the blue end of the Mix2Vial transfer set firmly through the center of the stopper of the diluent vial (Figure 2).	 Figure 2
6. Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package and not the Mix2Vial transfer set (Figure 3).	 Figure 3
7. With the Humate-P vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and push the plastic spike of the transparent adapter firmly through the center of the stopper of the Humate-P vial (Figure 4). The diluent will automatically transfer into the Humate-P vial.	 Figure 4
8. With the diluent and Humate-P vial still attached to the Mix2Vial transfer set, gently swirl the Humate-P vial to ensure the Humate-P is fully dissolved (Figure 5). Do not shake the vial.	 Figure 5

9. With one hand grasp the Humate-P side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set, and unscrew the set into two pieces (Figure 6).	 Figure 6
10. Draw air into an empty, sterile syringe. While the Humate-P vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the Humate-P vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly (Figure 7).	 Figure 7
11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Figure 8). Attach the syringe to a suitable intravenous administration set.	 Figure 8
12. If patient requires more than one vial, pool the contents of multiple vials into one syringe. Use a separate unused Mix2Vial for each product vial.	

- The solution should be clear or slightly opalescent. After filtering/withdrawal the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Even if the directions for use for the reconstitution procedure are precisely followed, it is not uncommon for a few flakes or particles to remain. The filter included in the Mix2Vial device removes those particles completely. Filtration does not influence dosage calculations. Do not use visibly cloudy solutions or solutions still containing flakes or particles after filtration.
- Do not refrigerate Humate-P after reconstitution. Administer within 3 hours after reconstitution.
- Slowly infuse the solution (maximally 4 mL/minute) with a suitable intravenous administration set.
- Discard the administration equipment and any unused Humate-P after use.

3 DOSAGE FORMS AND STRENGTHS

Humate-P is available as a sterile, lyophilized powder for intravenous administration following reconstitution. Each vial of Humate-P contains the labeled amount of VWF:RCo and FVIII activity expressed in International Units (IU). The average ratio of VWF:RCo to FVIII is 2.4:1.

Approximate potencies are shown below; check each carton/vial for the actual potency prior to reconstitution:

VWF:RCo/vial	FVIII/vial	Diluent
600 IU	250 IU	5 mL
1200 IU	500 IU	10 mL
2400 IU	1000 IU	15 mL

IU = International Units.

4 CONTRAINDICATIONS

Humate-P is contraindicated in individuals who have had an anaphylactic or severe systemic reaction to antihemophilic factor or von Willebrand factor preparations.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Events (VWD Patients)

Thromboembolic events have been reported in VWD patients receiving Antihemophilic Factor/von Willebrand Factor Complex replacement therapy, especially in the setting of known risk factors for thrombosis.[3,4] Early reports indicate a higher incidence may occur in females. Endogenous high levels of FVIII have also been associated with thrombosis, but no causal relationship has been established. Exercise caution and consider antithrombotic measures in all at-risk VWD patients who are receiving coagulation factor replacement therapy.

5.2 Monitoring for Intravascular Hemolysis

Humate-P contains blood group isoagglutinins (anti-A and anti-B). When doses are very large or need to be repeated frequently (for example, when inhibitors are present or when pre- and post-surgical care is involved), monitor patients of blood groups A, B, and AB for signs of intravascular hemolysis and decreasing hematocrit values and treat appropriately.

5.3 Monitoring VWF:RCo and FVIII Levels

Monitor the VWF:RCo and FVIII levels of VWD patients receiving Humate-P using standard coagulation tests, especially in cases of surgery. It is advisable to monitor trough VWF:RCo and FVIII:C levels at least once a day in order to adjust the dosage of Humate-P as needed to avoid excessive accumulation of coagulation factors [*see Dosage and Administration (2.2, 2.3)*].

5.4 Transmission of Infectious Agents

Humate-P is made from human plasma. Products made from human plasma may contain infectious agents (e.g., viruses and theoretically, the Creutzfeldt-Jakob disease [CJD] agent) that can cause disease [*see Description (11) and Patient Counseling Information (17)*]. 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 current virus infections, and by inactivating and/or removing certain viruses during manufacturing [*see Description (11)*].

Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Thus the risk of transmission of infectious agents cannot be eliminated completely. **Report all infections thought by a physician possibly to have been transmitted by this product to CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

Some viruses, such as Parvovirus B19 virus (B19V) or hepatitis A (HAV), are particularly difficult to remove or inactivate. B19V may most seriously affect pregnant women and immune-compromised individuals.

Although the overwhelming number of B19V and HAV cases are community acquired, reports of these infections have been associated with the use of some plasma-derived products. Therefore, physicians should be alert to the potential symptoms of B19V and HAV infections [*see Patient Counseling Information (17)*].

Symptoms of B19V may include low-grade fever, rash, arthralgia, and transient symmetric, nondestructive arthritis. Diagnosis is often established by measuring B19V-specific IgM and IgG antibodies. Symptoms of HAV include low-grade fever, anorexia, nausea, vomiting, fatigue, and jaundice. A diagnosis may be established by measuring specific IgM antibodies.

Physicians should strongly consider administration of hepatitis A and hepatitis B vaccines to individuals receiving plasma derivatives. Potential risks and benefits of vaccination should be weighed by the physician and discussed with the patient.

6 ADVERSE REACTIONS

The most serious adverse reaction observed in patients receiving Humate-P is anaphylaxis. Thromboembolic events have also been observed in patients receiving Humate-P for the treatment of VWD [*see Warnings and Precautions (5.1)*]. Reports of thromboembolic events in VWD patients with other thrombotic risk factors receiving coagulation factor replacement therapy have been obtained from spontaneous reports, published literature, and a European clinical study. In some cases, inhibitors to coagulation factors may occur. However, no inhibitor formation was observed in any of the clinical studies.

In patients receiving Humate-P in clinical studies for treatment of VWD, the most commonly reported adverse reactions observed by >5% of subjects are allergic-anaphylactic reactions (including urticaria, chest tightness, rash, pruritus, and edema). For patients undergoing surgery, the most common adverse reactions are postoperative wound and injection-site bleeding, and epistaxis.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Treatment of Bleeding Episodes in VWD

Allergic symptoms, including allergic reaction, urticaria, chest tightness, rash, pruritus, and edema, were reported in 6 of 97 (6%) subjects in a Canadian retrospective study [*see Clinical Studies (14.1)*]. Four of 97 (4%) subjects experienced seven adverse events that were considered to have a possible or probable relationship to Humate-P. These included chills, phlebitis, vasodilation, paresthesia, pruritus, rash, and urticaria. All were mild in intensity with the exception of a moderate case of pruritus.

In a prospective, open-label safety and efficacy study of Humate-P in VWD subjects with serious life- or limb-threatening bleeding or undergoing emergency surgery, seven of 71 (10%) subjects experienced nine adverse reactions. These were one occurrence each of mild vasodilation and mild pruritis; two occurrences of mild paresthesia; and one occurrence each of moderate peripheral edema and extremity pain and severe pseudothrombocytopenia (platelet clumping with a false low reading). Humate-P was discontinued in the subject who experienced the peripheral edema and extremity pain.

Prevention of Excessive Bleeding During and After Surgery in VWD

Among the 63 VWD subjects who received Humate-P for prevention of excessive bleeding during and after surgery, including one subject who underwent colonoscopy without the planned polypectomy, the most common adverse events were postoperative hemorrhage (35 events in 19 subjects with five subjects experiencing bleeding at up to three different sites), postoperative nausea (15 subjects), and postoperative pain (11 subjects). Table 5 presents the postoperative hemorrhagic adverse events.

Table 5. Hemorrhagic Adverse Events in 63 Surgical Subjects

Adverse Event	Surgical Procedure Category	Number of Subjects/ Events	Onset* (Number of Events)		Severity (Number of Events)		
			On	Post	Mild	Mod	Severe
Wound/injection site bleeding	Major	8/11	7	4	9	–	2
	Minor	2/2	2	–	1	1	–
	Oral	2/6	–	6	3	3	–
Epistaxis	Major	4/4	2	2	3	1	–
	Minor	1/1	1	–	1	–	–
Cerebral hemorrhage/ subdural hematoma	Major	1/2	2†	–	–	2	–
Gastrointestinal bleeding	Major	1/3	3‡	–	–	2	1
Menorrhagia	Major	1/1	1§	–	–	1	–
Groin bleed	Oral	1/1	–	1	1	–	–
Ear bleed	Major	1/1	1	–	1	–	–
Hemoptysis	Major	1/1	1	–	1	–	–
Hematuria	Major	1/1	1	–	1	–	–
Shoulder bleed	Major	1/1	1	–	1	–	–

* On = on-therapy; onset while receiving Humate-P or within 1 day of completing Humate-P administration. Post = post-therapy; onset at least one day after completing Humate-P administration.
† Reported as serious adverse events following intracranial surgery.
‡ Two of these events were reported as serious adverse events following gastrojejunal bypass.
§ Reported as a serious adverse event requiring hysterectomy following hysteroscopy and dilation and curettage.

Table 6 lists the non-hemorrhagic adverse events reported in at least two subjects, regardless of causality, and the adverse events that were possibly related to Humate-P. Pulmonary embolus considered possibly related to Humate-P occurred in one elderly subject who underwent bilateral knee replacement.

Table 6. Non-Hemorrhagic and Possibly Related Adverse Events in 63 Surgical Subjects

Body System	Adverse Event (AE)	Number of Subjects With an AE Possibly Related to Humate-P	Number of Subjects With an AE Regardless of Causality*
Body as a whole	Pain	–	11
	Fever	–	4
	Abdominal pain	–	3
	Infection	–	3
	Surgery	–	3
	Back pain	–	2
	Facial edema	–	2
Cardiovascular	Chest pain	–	3
	Pulmonary embolus†	1	1
	Thrombophlebitis†	1	1
Digestive	Nausea	1	15
	Constipation	–	7
	Vomiting	1	3
	Sore throat	–	2
Hemic and lymphatic system	Anemia/decreased hemoglobin	–	2
Metabolic/ nutritional	Increased SGPT	1	1
Nervous	Dizziness	1	5
	Headache	1	4
	Increased sweating	–	3
	Insomnia	–	2
Skin and appendages	Pruritus	–	3
	Rash	1	1
Urogenital	Urinary retention	–	4
	Urinary tract infection	–	2

* Events occurring in two or more subjects.
† Events occurring in separate subjects.

Eight subjects experienced 10 postoperative serious adverse events: one with subdural hematoma and intracerebral bleeding following intracranial surgery related to an underlying cerebrovascular abnormality; one with two occurrences of gastrointestinal bleeding following gastrojejunal bypass; and one each with sepsis, facial edema, infection, menorrhagia requiring hysterectomy following hysteroscopy and dilation and curettage, pyelonephritis, and pulmonary embolus.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Humate-P. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequ ency or establish a causal relationship to Humate-P exposure.

Adverse reactions reported in patients receiving Humate-P for treatment of VWD or hemophilia A are allergic-anaphylactic reactions (including urticaria, chest tightness, rash, pruritus, edema, and shock), development of inhibitors to FVIII, and hemolysis. Additional adverse reactions reported for VWD are thromboembolic complications, chills and fever, and hypervolemia.

7 DRUG INTERACTIONS

None reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.2 Labor and Delivery

It is not known whether Humate-P can cause harm to the mother or the fetus when administered during labor and delivery. Humate-P should be given during labor and delivery only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Humate-P is administered to a nursing woman.

8.4 Pediatric Use

Hemophilia A

Adequate and well-controlled studies with long-term evaluation of joint damage have not been done in pediatric subjects. Joint damage may result from suboptimal treatment of hemarthroses.

VWD

The safety and effectiveness of Humate-P for the treatment of VWD was demonstrated in 26 pediatric subjects, including infants, children, and adolescents, but have not been evaluated in neonates. The safety of Humate-P for the prevention of excessive bleeding during and after surgery was demonstrated in eight pediatric subjects (ages 3 to 15) with VWD. Of the 34 pediatric subjects studied for either treatment of bleeding episodes in VWD or prevention of excessive bleeding during and after surgery, four were infants (1 month to under 2 years of age), 23 were children (2 through 12 years), and seven were adolescents (13 through 15 years).

As in adults, pediatric patients should be dosed based on body weight (kg) [*see Dosage and Administration (2.2, 2.3)*].

8.5 Geriatric Use

Clinical studies of Humate-P did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

11 DESCRIPTION

Humate-P, Antihemophilic Factor/von Willebrand Factor Complex (Human), is a purified, sterile, lyophilized concentrate of Factor VIII (FVIII) and von Willebrand Factor (VWF) (Human) for intravenous administration in the treatment of patients with classical hemophilia (hemophilia A) and VWD [*see Clinical Pharmacology (12)*].

Humate-P is purified from the cold insoluble fraction of pooled human plasma. The pooled human plasma used to produce Humate-P is collected from licensed facilities in the United States (US). All source plasma used in the manufacture of Humate-P is tested by FDA-licensed Nucleic Acid Tests (NAT) for hepatitis C virus (HCV), human immunodeficiency virus-1 (HIV-1), hepatitis A virus (HAV), and hepatitis B virus (HBV) and found to be nonreactive (negative).

Each vial of Humate-P contains the labeled amount of von Willebrand Factor:Ristocetin Cofactor (VWF:RCo) and FVIII activity expressed in International Units (IU) [*see Dosage Forms and Strengths (3)*], as defined by the current international standard established by the World Health Organization. One International Unit (IU) of VWF:RCo or FVIII is approximately equal to the amount of VWF:RCo or FVIII in 1.0 mL of fresh-pooled human plasma. The average ratio of VWF:RCo to FVIII is 2.4:1.Fibrinogen content in Humate-P is less than or equal to 0.2 mg/mL. Humate-P contains anti-A and anti-B blood group isoagglutinins [*see Warnings and Precautions (5.2)*].

When reconstituted with the volume of Sterile Water for Injection, USP provided, each mL of Humate-P contains 72 to 224 International Units (IU) VWF:RCo activity,* 40 to 80 International Units (IU) FVIII activity, 15 to 33 mg of glycine, 3.5 to 9.3 mg of sodium citrate, 2 to 5.3 mg of sodium chloride, 8 to 16 mg of Albumin (Human), 2 to 14 mg of other proteins, and 10 to 20 mg of total proteins. Humate-P contains no preservative.

*This correlates to a VWF:RCo to FVIII activity average ratio of 2.4:1, which is used to calculate the nominal values of VWF:RCo activity and is the average VWF:RCo activity.

The manufacturing procedure for Humate-P includes multiple processing steps that reduce the risk of virus transmission. The virus inactivation/removal capacity consists of four steps:

- Cryoprecipitation
- Al(OH)3 adsorption, glycine precipitation, and NaCl precipitation, studied in combination
- Heat treatment at 60°C for 10 hours in aqueous solution
- Lyophilization

The total cumulative virus reductions range from 6.0 to ≥11.7 $\log_{10}$ as shown in Table 7.

Table 7. Cumulative Virus Reduction Factors for Humate-P

Manufacturing Step	Virus Reduction Factor ($\log_{10}$)						
	Enveloped Viruses				Non-Enveloped Viruses		
	HIV-1	BVDV	PRV	WNV	HAV	CPV	B19V
Cryoprecipitation	ND	ND	1.6	ND	ND	1.9	ND
$Al(OH)_3$ Adsorption/ Glycine Precipitation/ NaCl Precipitation	3.8	2.8	3.9	ND	2.3	3.0	ND
Heat Treatment*	≥6.4	≥8.9	4.7	≥7.8	4.2	1.1	≥3.9†
Lyophilization	ND	ND	ND	ND	1.3	ND	ND
Cumulative Virus Reduction [$\log_{10}$]	**≥10.2**	**≥11.7**	**10.2**	**NA**	**7.8**	**6.0**	**NA**

HIV-1, human immunodeficiency virus type 1, model for HIV-1 and HIV-2
BVDV, bovine viral diarrhea virus, model for HCV
PRV, pseudorabies virus, model for large enveloped DNA viruses
WNV, West Nile virus
HAV, hepatitis A virus
CPV, canine parvovirus, model for B19V
B19V, human parvovirus B19
ND, not determined
NA, not applicable
* At 60°C for 10 hours in aqueous solution.
† The virus evaluation studies for B19V employed a novel experimental infectivity assay using a clone of the cell line UT7 that contains erythropoietic progenitor cells; (residual) virus titer was determined using an immunofluorescence-based detection method.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active components of Humate-P consist of two different noncovalently bound proteins (FVIII and VWF). FVIII is an essential cofactor in activation of factor X, leading ultimately to the formation of thrombin and, subsequently, fibrin. VWF promotes platelet aggregation and platelet adhesion on damaged vascular endothelium; activated platelets interact with clotting proteins to form a clot. VWF also serves as a stabilizing carrier protein for the procoagulant protein FVIII.[5,6] The activity of VWF is measured as VWF:RCo.

12.3 Pharmacokinetics

Hemophilia A

After infusion of Humate-P, a rapid increase of plasma FVIII:C is followed by a rapid decrease in activity and, subsequently, a slower rate of decrease in activity. Studies with Humate-P in subjects with hemophilia A have demonstrated a mean half-life of 12.2 (range: 8.4 to 17.4) hours.

VWD

The pharmacokinetics of Humate-P were studied in 41 subjects in a US study and in 28 subjects in a European study [*see Clinical Studies (14.2)*]. In both studies, subjects were evaluated in the nonbleeding state prior to a surgical procedure. Table 8 summarizes the pharmacokinetics of Humate-P based on these studies. Wide inter-subject variability was observed in pharmacokinetic values obtained from these studies.

Table 8. Pharmacokinetics of Humate-P in Two Studies of Subjects in the Non-Bleeding State Prior to Surgery

	US Study	European Study
Number of subjects	41	28
Type 1 VWD	16	10
Type 2A VWD	2	10
Type 2B VWD	4	--
Type 2M VWD	6	1
Type 3 VWD	13	7
Dosage of Humate-P	60 IU VWF:RCo/kg BW	80 IU VWF:RCo/kg BW
Median terminal half-life of VWF:RCo (range)	11 hours* (3.5-33.6)	10 hours† (2.8-28.3)
Median clearance (range)	3.1 mL/hr/kg (1-16.6)	4.8 mL/hr/kg (2.1-53)
Volume of distribution at steady state (range)	53 mL/kg (29-141)	59 mL/kg (32-290)
Median IVR for VWF:RCo activity (range)	2.4 IU/dL per IU/kg (1.1-4.2)	1.9 IU/dL per IU/kg (0.6-4.5)

IU = International Units.
BW = body weight.
* Excluding 5 subjects with a half-life exceeding the blood sampling time of 24 or 48 hours.
† Excluding 1 subject with a half-life exceeding the blood sampling time of 48 hours.

Humate-P has been demonstrated in several studies to contain the high molecular weight multimers of VWF. The presence of a multimeric composition of VWF in Humate-P is similar to that found in normal plasma and this component is considered to be important for correcting the coagulation defect in patients with VWD.[7,8]

The multimeric patterns of Humate-P in the US study were measured in 13 subjects with type 3 VWD; 11 had absent or barely detectable multimers at baseline. Of those 11 subjects, all had some high molecular weight multimers present 24 hours after infusion of Humate-P. In the European study, infusion of Humate-P corrected the defect of the multimer pattern in subjects with types 2A and 3 VWD. High molecular weight multimers were detectable until at least 8 hours after infusion.

Based on the small sample size evaluation, it appears that age, sex, and type of VWD have no impact on the pharmacokinetics of VWF:RCo.

14 CLINICAL STUDIES

Controlled clinical studies to evaluate the safety and efficacy of prophylactic dosing with Humate-P to prevent spontaneous bleeding have not been conducted in VWD subjects. Adequate data are not presently available on which to evaluate or to base dosing recommendations in this setting.

14.1 Treatment of Bleeding Episodes in VWD

Clinical efficacy of Humate-P in the control of bleeding in subjects with VWD was determined by a retrospective review of clinical safety and efficacy data obtained from 97 Canadian VWD subjects who received product under an Emergency Drug Release Program. The dosage schedule and duration of therapy were determined by the medical practitioner.

There were 514 requests for product use for surgery, bleeding, or prophylaxis in the 97 subjects. Of these, Humate-P was not used in 151 cases, and follow-up safety and/or efficacy information was available for 303 (83%) of the remaining 363 requests. In many cases, Humate-P from a single request was used for several treatment courses in one subject. Therefore, there are more reported treatment courses than requests.

Humate-P was administered to 97 subjects in 530 treatment courses: 73 for surgery, 344 for treatment of bleeding, and 20 for prophylaxis of bleeding. The majority of the 93 "other" uses involved dental procedures, diagnostic procedures, prophylaxis prior to a procedure, or test doses.

Table 9 summarizes the dosing information (all subjects) for bleeding episodes.

Table 9. Dosing Information for Bleeding Episodes in VWD

		Type/Location of Bleeding Episode				
		Digestive System	Nose+Mouth +Pharynx	Integument System	Female Genital System	Musculo-skeletal
No. of Subjects		14	29	11	4	22
Loading Dose	Mean Dose (SD)*	62.1 (31.1)	66.9 (24.3)	73.4 (37.7)	88.5 (28.3)	50.2 (24.9)
	No. of Infusions†	37	127	22	7	107
Maintenance Dose	Mean Dose (SD)*	61.5 (38.0)	67.5 (22.4)	56.5 (63.3)	74.5 (17.7)	63.8 (28.8)
	No. of Infusions†	250	55	4	15	121
No. of Treatment Days per Bleeding Episode	Mean (SD)	4.6 (3.6)	1.4 (1.2)	1.1 (0.4)	2.8 (2.9)	2.0 (1.9)
	No. of Events	49	130	22	9	108
No. of Infusions by Treatment Day						
No. of Subjects		14	29	11	4	22
Day 1‡	Mean (SD)	1.2 (0.4)	1.1 (0.2)	1.0 (0.2)	1.0 (0.0)	1.0 (0.1)
	No. of Events	49	130	22	9	108
No. of Subjects		13	9	3	1	15
Day 2	Mean (SD)	1.2 (0.6)	1.3 (0.5)	1.0 (0.0)	1.0 (-)	1.2 (0.5)
	No. of Events	41	12	3	1	26
No. of Subjects		12	6	-	2	10
Day 3	Mean (SD)	1.5 (0.8)	1.4 (0.7)	-	1.0 (0.0)	1.2 (0.4)
	No. of Events	25	9	-	3	18

SD, standard deviation.
* IU VWF:RCo/kg.
† Number of infusions where the dose per kg body weight was available.
‡ Day 1, first treatment day.

14.2 Prevention of Excessive Bleeding During and After Surgery in VWD

Two prospective, open-label, non-controlled, multicenter clinical studies, one in the US and one in Europe, investigated the safety and hemostatic efficacy of Humate-P in subjects with VWD undergoing surgery.

- **US clinical study** – The primary objective of this study was to demonstrate the safety and hemostatic efficacy of Humate-P in preventing excessive bleeding in adult and pediatric subjects with VWD undergoing surgery. The 35 subjects (21 female and 14 male) ranged in age from 3 to 75 years (mean 32.9); seven were age 15 or younger and two were age 65 or older. Twelve subjects had type 1 VWD, two had type 2A, three had type 2B, five had type 2M, and 13 had type 3. Twenty-eight of the surgical procedures were classified as major (e.g., orthopedic joint replacement, intracranial surgery, multiple tooth extractions, laparoscopic cholecystectomy), four as minor (e.g., placement of intravenous access device), and three subjects had oral surgery.* Seven of the 13 subjects with type 3 VWD had major surgery.

  The first 15 subjects received a loading dose of Humate-P corresponding to 1.5 times the "full dose" (defined as the dose predicted to achieve a peak VWF:RCo level of 100 International Units (IU)/dL as determined by each subject's calculated IVR and baseline VWF:RCo level); the loading dose did not vary with the type of surgery performed (i.e., major, minor, or oral). The remaining 20 subjects were dosed based on individual pharmacokinetic assessments and target peak VWF:RCo levels of 80 to 100 International Units (IU)/dL for major surgery and 50 to 60 International Units (IU)/dL for minor or oral surgery, respectively. All 35 subjects received initial maintenance doses corresponding to 0.5 times the full dose at intervals of 6, 8, or 12 hours after surgery as determined by their individual half-lives for VWF:RCo; subsequent maintenance doses were adjusted based on regular measurements of trough VWF:RCo and FVIII:C levels. The median duration of treatment was 1 day (range: 1 to 2 days) for oral surgery, 5 days (range: 3 to 7 days) for minor surgery, and 5.5 days (range: 2 to 26 days) for major surgery.

- **European clinical study** – The primary objective of this study was to assess the ability of Humate-P to effectively correct the coagulation defect in subjects with VWD undergoing elective surgery, as demonstrated by an increase in VWF:RCo and FVIII, a shortening of the prolonged bleeding time, and the prevention and/or cessation of excessive bleeding. This study did not have a pre-stated hypothesis to evaluate hemostatic efficacy. The 27 subjects (18 females and nine males) ranged in age from 5 to 81 years (median age: 46 years); one was age 5, and five were older than 65. Ten subjects had type 1 VWD, nine had type 2A, one had type 2M, and seven had type 3. Sixteen of the surgical procedures were classified as major (orthopedic joint replacement, hysterectomy, multiple tooth extractions, laparoscopic adnexectomy, laparoscopic cholecystectomy, and basal cell carcinoma excision). Six of the seven subjects with type 3 VWD had major surgery.

  Dosing was individualized based on a pharmacokinetic assessment performed before surgery. The median duration of treatment was 3.5 days (range: 1 to 17 days) for minor surgery and 9 days (range: 1 to 17 days) for major surgery.

In both studies, assessments of the hemostatic efficacy of Humate-P in preventing excessive bleeding were performed at the end of surgery, 24 hours after the last infusion of Humate-P, and at the end of the study (14 days following surgery).

Table 10 summarizes the end-of-surgery hemostatic efficacy assessments in subjects participating in either the US or European study.

Table 10. Investigator's End-of-Surgery Hemostatic Efficacy Assessments for the US and European Surgical Studies

	Number of Subjects	End-of-Surgery Hemostatic Efficacy Assessments	
		Effective (Excellent / Good)*	95% Confidence Interval (CI) for Effective Proportion†
US study	35	32 (91.4%)	78.5-97.6%
European study	26‡	25 (96%)	82-99.8%

* Excellent: Hemostasis clinically not significantly different from normal.
Good: Mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing).

† 95% CIs according to Blyth-Still-Casella.

‡ One subject with missing information.

Table 11 summarizes the overall hemostatic efficacy assessments in subjects participating in either the US or European study. Humate-P was effective in preventing excessive bleeding during and after surgery.

* Oral surgery is defined as extraction of fewer than three teeth, if the teeth are non-molars and have no bony involvement. Extraction of more than one impacted wisdom tooth is considered major surgery due to the expected difficulty of the surgery and the expected blood loss, particularly in subjects with type 2A or type 3 VWD. Extraction of more than two teeth is considered major surgery in all patients.

Table 11. Investigator's Overall Hemostatic Efficacy Assessments for the US and European Surgical Studies

	Number of Subjects	Overall Hemostatic Assessments	
		Effective (Excellent / Good)*	95% CI for Effective Proportion†
US study‡	35	35 (100%)	91.3-100%
European study§	27	26 (96.3%)	82.5-99.8%

* Excellent: Hemostasis clinically not significantly different from normal.
Good: Mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing).

† 95% CIs according to Blyth-Still-Casella.

‡ Overall hemostatic efficacy was assessed 24 hours after the last Humate-P infusion or 14 days after surgery, whichever came earlier.

§ Overall hemostatic efficacy was not prospectively defined for the European study; the efficacy result displayed is the least efficacious ranking assigned by an investigator between surgery and Day 14.

In the US study, all efficacy assessments were reviewed by an independent Data Safety Monitoring Board (DSMB). The DSMB agreed with the investigators' assessments of the overall hemostatic efficacy for all but two subjects (neither of whom had type 3 VWD). Based on this, the DSMB judged hemostatic efficacy as "effective" in 33 (94.3%) (95% CI: 81.1% to 99.0%) of the 35 subjects.

In the US study, the median actual estimated blood loss did not exceed the median expected blood loss, regardless of the type of surgery. Table 12 shows the median expected and actual estimated blood loss during surgery in the US study.

Table 12. Expected and Actual Estimated Blood Loss During Surgery in the US Study

Estimated Blood Loss	Oral Surgery (n=3)	Minor Surgery (n=4)	Major Surgery (n=28)	Total (n=35)
Expected – Median (range) mL	10 (5-50)	8 (0-15)	50 (0-300)*	20 (0-300)*
Actual – Median (range) mL	3 (0-15)	3 (0-10)	26 (0-300)†	18 (0-300)†

* One subject with missing information

† Five subjects with missing information

In the US study, four subjects received transfusions, three due to adverse events and one due to pre-existing anemia. In the European study, one subject received transfusions to treat pre-existing anemia.

14.3 Virus Transmission Studies

Clinical evidence of the absence of virus transmission in Humate-P was obtained in additional studies.

In one study, none of the evaluable subjects (31 of 67) who received Humate-P developed HBV infection or showed clinical signs of non-A, non-B (NANB) hepatitis infection.

In another study, 32 lots of Humate-P were administered to 26 subjects with hemophilia or VWD who had not previously received any blood products. No subject developed any signs of an infectious disease, and the 10 subjects not previously vaccinated remained seronegative for markers of infection with HBV, HAV, cytomegalovirus (CMV), Epstein-Barr virus, and HIV.

In a retrospective study, 155 subjects evaluated remained negative for the presence of HIV-1 antibodies for time periods ranging from 4 months to 9 years from the initial administration of Humate-P. All 67 of the subjects tested for HIV-2 antibodies remained seronegative.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

- Humate-P is supplied in a single-use vial containing the labeled amount of VWF:RCo and FVIII activity expressed in International Units (IU).
- The components used in the packaging for Humate-P contain no latex.
- When stored at temperatures up to 25°C (77°F), Humate-P is stable for 36 months up to the expiration date printed on its label. Do not freeze.
- Humate-P does not contain a preservative and should be used within 3 hours after reconstitution.

Each product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
600 IU VWF:RCo and 250 IU FVIII	63833-615-02	• Humate-P in a single-use vial [NDC 63833-625-01] • 5 mL vial of Sterile Water for Injection, USP [NDC 63833-765-53] • Mix2Vial transfer set
1200 IU VWF:RCo and 500 IU FVIII	63833-616-02	• Humate-P in a single-use vial [NDC 63833-626-01] • 10 mL vial of Sterile Water for Injection, USP [NDC 63833-765-54] • Mix2Vial transfer set
2400 IU VWF:RCo and 1000 IU FVIII	63833-617-02	• Humate-P in a single-use vial [NDC 63833-627-01] • 15 mL vial of Sterile Water for Injection, USP [NDC 63833-765-55] • Mix2Vial transfer set

17 PATIENT COUNSELING INFORMATION

Inform patients that Humate-P is made from human plasma (part of the blood) and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the risk that Humate-P may transmit an infectious agent has been reduced by screening plasma donors, by testing the donated plasma for certain virus infections, and by inactivating and/or removing certain viruses during manufacturing [*see Warnings and Precautions (5.4)*].

Inform patients that some viruses, such as B19V and HAV, may be particularly difficult to remove or inactivate. Advise patients, especially pregnant women and immune-compromised individuals, to report low-grade fever, rash, joint pain, anorexia, nausea, vomiting, fatigue, and jaundice [*see Warnings and Precautions (5.4)].*

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