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

ZLB Behring

℞ only

DESCRIPTION

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® is a stable, purified, sterile, lyophilized concentrate of Antihemophilic Factor (Human) and von Willebrand Factor (VWF) (Human) to be administered by the intravenous route in the treatment of patients with classical hemophilia (hemophilia A) and von Willebrand disease (VWD) (see **CLINICAL PHARMACOLOGY**).

Humate-P® is purified from the cold insoluble fraction of pooled human fresh-frozen plasma and contains highly purified and concentrated Antihemophilic Factor/von Willebrand Factor Complex (Human). Humate-P® has a high degree of purity with a low amount of non-factor proteins. Fibrinogen is less than or equal to 0.1 mg/mL. Humate-P® has a higher Factor potency than cryoprecipitate preparations. Each vial of Humate-P® contains the labeled amount of Factor VIII activity in international units. Additionally, each vial of Humate-P® also contains the labeled amount of von Willebrand Factor:Ristocetin Cofactor (VWF:RCo) activity expressed in IU (see **DOSAGE AND ADMINISTRATION**). An international unit (IU) is defined by the current international standard established by the World Health Organization. One IU Factor VIII or 1 IU VWF:RCo is approximately equal to the level of Factor VIII or VWF:RCo found in 1.0 mL of fresh-pooled human plasma.

Upon reconstitution with the volume of diluent provided (Sterile Diluent for Humate-P®), each mL of Humate-P® contains 20 to 40 IU Factor VIII activity, 50 to 100 IU VWF:RCo activity, 15 to 33 mg of glycine, 3.5 to 9.3 mg of sodium citrate, 2 to 5.3 mg of sodium chloride, 4 to 8 mg of Albumin (Human), 1 to 7 mg of other proteins and 5 to 15 mg of total proteins.

This product is prepared from pooled human plasma collected from U.S. licensed facilities in the U.S.

Humate-P® is heat-treated in aqueous solution at 60°C for 10 hours.[1] This pasteurization protocol has been shown *in vitro* to inactivate both enveloped (e.g., Human Immunodeficiency Virus [HIV], Herpes Simplex Virus [HSV-1], Bovine Viral Diarrhea Virus [BVDV], and Cytomegalovirus [CMV]) and non-enveloped (e.g., Poliovirus) viruses. However, no procedure has been shown to be totally effective in removing the risk of viral infectivity from coagulant factor concentrates (see **CLINICAL PHARMACOLOGY** and **WARNINGS**).

The plasma used in the manufacture of this product has been tested and found negative for HBV, HCV, and HIV-1 by an investigational test procedure referred to as Nucleic Acid Testing (NAT) using Polymerase Chain Reaction (PCR) Technology. Investigational testing is being performed to determine the effectiveness of NAT to detect low levels of viral material. The significance of a negative result is unknown since the effectiveness of the test has not been established.

Humate-P® has been demonstrated in several studies to contain the high molecular weight multimers of VWF. This component is considered to be important for correcting the coagulation defect in patients with VWD (see **CLINICAL PHARMACOLOGY**).

Humate-P® contains anti-A and anti-B blood group isoagglutinins (see **PRECAUTIONS**).

Viral Reduction Capacity

The pasteurization process (10 hours at 60°C in aqueous solution) used in the manufacture of this concentrate has been shown to inactivate *in vitro* HIV and several model viruses. In each experiment, inactivation to undetectable levels was achieved in considerably less than 10 hours. In replicate studies, HIV was reduced by ≥5.6, ≥6.3 and ≥6.8 $\log_{10}$, respectively, to undetectable levels. In addition to HIV, studies were also performed using three lipid enveloped model viruses (HSV-1, BVDV and CMV), and one non-enveloped virus (Poliovirus). HSV-1 was reduced by ≥5.8, ≥7.2 and ≥7.3 $\log_{10}$, respectively, to undetectable levels in three replicate experiments; BVDV was reduced by ≥4.8 and ≥5.4 $\log_{10}$ to undetectable levels in two replicate experiments; and CMV was reduced by ≥6.0 $\log_{10}$ to an undetectable level in one experiment. In the case of Poliovirus, a non-enveloped virus, reduction by ≥7.1 and ≥7.3 $\log_{10}$ to undetectable levels in two replicate experiments was observed.

The viral reduction capacity of the purification and preparative steps employed in the production of Humate-P®, exclusive of the pasteurization protocol, has also been evaluated in *in vitro* experiments using HIV, HSV-1 and Poliovirus. In duplicate experiments, the mean cumulative reduction capacity for the processing steps evaluated was found to be the following: ≥10.8 $\log_{10}$ for HIV, ≥11.1 $\log_{10}$ for HSV-1 and ≥9.1 $\log_{10}$ for the non-enveloped virus Poliovirus.

The results of the validation studies described above document a mean cumulative total process viral reduction capacity of ≥17.0 $\log_{10}$ for HIV, ≥17.8 $\log_{10}$ for HSV-1 and ≥16.3 $\log_{10}$ for Poliovirus for the manufacturing steps evaluated (inclusive of pasteurization).

In vivo experiments of infectivity on chimpanzees[2] have confirmed the reliability of the manufacturing process, including the pasteurization method, in reducing the risk of transmission of hepatitis. Two chimpanzee studies were used to evaluate the efficacy of the manufacturing process in inactivating experimentally added hepatitis B virus, and one chimpanzee study evaluated the efficacy of the manufacturing process in inactivating experimentally added hepatitis C virus, as represented by agents of non-A, non-B (NANB) hepatitis from the Hutchinson pool.[2] In the first two studies, cryoprecipitate infected with hepatitis B virus, to yield a concentration of 3000 infectious units/mL, was injected into chimpanzees followed for six months or longer. All chimpanzees injected with either cryoprecipitate (n=4) or non-pasteurized Antihemophilic Factor/von Willebrand Factor Complex (Human) (n=4) developed hepatitis B markers (HBsAg, Anti-HBs, Anti-HBc). None of the seven chimpanzees injected with the pasteurized product became sero-positive. In an equivalent study of hepatitis C that utilized agents of NANB hepatitis from the Hutchinson pool[2] as the viral inoculum, four chimpanzees injected with pasteurized Antihemophilic Factor/von Willebrand Factor Complex (Human) product consistently remained serologically negative.

CLINICAL PHARMACOLOGY

General

The Antihemophilic Factor/VWF complex consists of two different noncovalently bound proteins (Factor VIII and von Willebrand factor). Factor VIII is an essential cofactor in activation of Factor X leading ultimately to formation of thrombin and fibrin. The VWF promotes platelet aggregation and platelet adhesion on damaged vascular endothelium; it also serves as a stabilizing carrier protein for the procoagulant protein Factor VIII.[3,4] The activity of VWF is measured as VWF:RCo.

Pharmacokinetics in Hemophilia A

After intravenous injection of Humate-P® in humans, there is a rapid increase of plasma Factor VIII activity (FVIII:C) followed by a rapid decrease in activity and a subsequent slower rate of decrease in activity. Studies with Humate-P® in hemophilic patients have demonstrated a mean half-life of 12.2 hours (range: 8.4 to 17.4 hours).

Pharmacokinetics in von Willebrand disease

Humate-P® has been demonstrated in several studies to contain the high-molecular-weight multimers of VWF. This component is reported to be important for correcting the coagulation defect in patients with VWD.[5-9]

When administered to patients with VWD (types 1, 2 [A, B, C], or 3)[13], bleeding time decreased.[6,9,10,11,12] This effect was correlated with the presence of a multimeric composition of VWF similar to that found in normal plasma.[6,8,9,10,12]

The pharmacokinetics of Humate-P® have been evaluated in 8 VWD patients [type 1, n=1; type 2, n=1; type 2A, n=4; type 3, n=2] in the non-bleeding state. The median half-life of VWF:RCo was 10.3 hours (range: 6.4 to 13.3 hours). The median *in vivo* recovery for VWF:RCo activity was 1.89 (IU/dL)/(IU/kg) [range: 1.10 to 2.74 (IU/dL)/(IU/kg)]. In all patients, the administration of Humate-P® resulted in a transient shortening of the bleeding time. Humate-P® was effective in improving the VWF multimer pattern in VWD patients and in most cases this improvement was sustained through 22 to 26 hours postinfusion.

Clinical Studies

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

There were 514 requests for product use for surgery, bleeding or prophylaxis in the 97 Canadian patients. Of these, product 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, product from one request was used for several treatment courses in one patient. Therefore, there are more reported treatment courses than requests.

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® was administered to 97 patients, in 530 treatment courses: 73 for surgery, 344 for treatment of bleeding and 20 for prophylaxis of bleeding. For 93 "other" uses, the majority involved dental procedures, diagnostic procedures, prophylaxis prior to a procedure, or a test dose.

A summary of the number of patients and bleeding episodes treated, by VWD type, and corresponding efficacy rating is provided in Table 1. The efficacy rating was excellent/good in 100% of bleeding episodes treated in type 1, 2A and 2B patients. In type 3 patients, 95% of the bleeding episodes were rated as excellent/good and a poor (or no) response was observed in the remaining 5% of bleeding episodes treated.

Table 1: Summary of efficacy for bleeding episodes - all patients

	Diagnosis							
	Type 1 VWD		Type 2A VWD		Type 2B VWD		Type 3 VWD	
NUMBER OF PATIENTS	13		2		10		21	
Excellent/good	13	100%	2	100%	10	100%	18	86%
Poor/none	–	–	–	–	–	–	3	14%
NUMBER OF EVENTS	32		17		60		208	
Excellent/good	32	100%	17	100%	60	100%	198	95%
Poor/none	–	–	–	–	–	–	10	5%

For pediatric patients a summary of the number of patients and bleeding episodes treated, by VWD type, and corresponding efficacy rating is provided in Table 2. The efficacy rating was excellent/good in 100% of bleeding episodes treated in infants (types 2A, 3), children (types 1, 2A, 2B) and adolescents (types 1, 2B). In type 3 children and adolescents, 90% and 96% of the bleeding episodes were rated as excellent/good and a poor/none response was observed in the remaining 10% and 4% of the bleeding episodes, respectively.

Table 2: Summary of efficacy for bleeding episodes - pediatric patients

	Diagnosis							
	Type 1 VWD		Type 2A VWD		Type 2B VWD		Type 3 VWD	
NUMBER OF PATIENTS	4		2		5		12	
Excellent/good	4	100%	2	100%	5	100%	9	75%
Poor/none	–	–	–	–	–	–	3	25%
NUMBER OF EVENTS	8		17		22		138	
Excellent/good	8	100%	17	100%	22	100%	128	93%
Poor/none	–	–	–	–	–	–	10	7%

The dosing information (all patients) for bleeding events is summarized in Table 3.

Table 3: Summary of dosing information for bleeding events

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

Day 1 = First treatment day ([1] Number of infusions where the dose per kg body weight was available)

Clinical evidence of the viral safety of Humate-P® was obtained in additional studies. In one study, all evaluable patients (31 of 67) who received Humate-P® remained HBs-antigen negative. None of the 31 patients developed hepatitis B infection or showed clinical signs of NANB hepatitis infection.[14]

In an additional study, a total of 32 lots of Humate-P® were administered to a cohort of 26 hemophilic or VWD patients who had not previously received any blood products. Markers for hepatitis B virus and liver enzymes (ALT and AST) were tested at regular intervals as recommended by the International Committee on Thrombosis and Hemostasis. The study showed no significant elevation in liver enzyme levels over an observation period ranging from 2 months to 12 months. The 10 patients not previously vaccinated remained seronegative for markers of hepatitis B infection as well as for markers of infection with hepatitis A virus, CMV, Epstein-Barr virus and HIV. No patient developed any signs of an infectious disease.[15]

In a retrospective study, all 155 patients evaluated remained negative for the presence of HIV-1 antibodies for time periods ranging from four months to nine years from initial administration of product. Sixty-seven of these patients were also tested for HIV-2 antibodies and all remained seronegative.[16]

INDICATIONS AND USAGE

Humate-P® is indicated (1) in adult patients for treatment and prevention of bleeding in hemophilia A (classical hemophilia) and (2) in adult and pediatric patients for treatment of spontaneous and trauma-induced bleeding episodes in severe von Willebrand disease, and in mild and moderate von Willebrand disease where use of desmopressin 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 and to prevent excessive bleeding related to surgery have not been evaluated in von Willebrand disease patients. Adequate data are not presently available on which to evaluate or to base dosing recommendations in either of these settings.

CONTRAINDICATIONS

None known.

WARNINGS

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.[17,18,19] Early reports might indicate a higher incidence in females. In addition, endogenous high levels of FVIII have also been associated with thrombosis but no causal relationship has been established. In all VWD patients in situations of high thrombotic risk receiving coagulation factor replacement therapy, caution should be exercised and antithrombotic measures should be considered. See also **DOSAGE AND ADMINISTRATION.**

Humate-P® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. 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 by inactivating and/or removing certain viruses during manufacture (see **DESCRIPTION** section for viral reduction measures). Despite these measures, such products can still potentially transmit disease. There is also the theoretical possibility that infectious agents not yet known or identified may be present in such products.

The manufacturing procedure for Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-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 Humate-P® manufacturing process is the heat treatment of the purified, stabilized aqueous solution at 60.0 +/- 1°C for 10 hours. In addition, the purification procedure (several precipitation steps) used in the manufacture of Humate-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 cannot 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 ZLB Behring at 800-504-5434 (in the U.S. and Canada). The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

It is important to determine that the coagulation disorder is caused by factor VIII or VWF deficiency, since no benefit in treating other deficiencies can be expected.

Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement therapy, especially in the setting of known risk factors for thrombosis. In these patients, caution should be exercised and antithrombotic measures should be considered.

This Humate-P® preparation contains blood group isoagglutinins (anti-A and anti-B). When very large or frequently repeated doses are needed, as when inhibitors are present or when pre- and post- surgical care is involved, patients of blood groups A, B and AB should be monitored for signs of intravascular hemolysis and decreasing hematocrit values and be treated appropriately as required.

The replacement therapy should be monitored with the aid of coagulation tests, especially in cases of major surgery.

Other precautions are as follows:

- The sterile filter spike should only be used to transfer solution from the preparation vial to a syringe or infusion bottle or bag. The sterile filter spike must not be used for injection.
- The administration equipment and any unused Humate-P® should be discarded.

Information for Patients

Some viruses, such as parvovirus B19 or hepatitis A, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect 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 may include low-grade fever, rash, arthralgias and transient symmetric, nondestructive arthritis. Diagnosis is often established by measuring B19 specific IgM and IgG antibodies. Symptoms of hepatitis A include low grade fever, anorexia, nausea, vomiting, fatigue and jaundice. A diagnosis may be established by determination of specific IgM antibodies.

Pregnancy Category C

Animal reproduction studies have not been conducted with Antihemophilic Factor/von Willebrand Factor (Human). 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.

Pediatric Use

Adequate and well-controlled studies with long term evaluation of joint damage have not been done in pediatric patients. Joint damage may result from suboptimal treatment of hemarthroses. For immediate control of bleeding for Hemophilia A, the general recommendations for dosing and administration for adults, found in the **DOSAGE AND ADMINISTRATION** section, may be referenced.

The safety and effectiveness of Humate-P® for the treatment of von Willebrand disease was demonstrated in 26 pediatric patients, including infants, children and adolescents but has not yet been evaluated in neonates. As in adults, pediatric patients should be dosed based upon weight (kg) in accordance to information in the **DOSAGE AND ADMINISTRATION** section.

Geriatric Use

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

ADVERSE REACTIONS

Humate-P® is usually tolerated without reaction. Rare cases of allergic reaction and rise in temperature have been observed. Anaphylactic reactions can occur in rare instances. If allergic/anaphylactic reactions occur, the infusion should be discontinued and appropriate treatment given as required. In some cases, inhibitors of Factor VIII may occur.

Allergic symptoms, including allergic reaction, urticaria, chest tightness, rash, pruritus, and edema, were reported in 6 of 97 (6%) of patients in a Canadian retrospective study. Two of 97 (2%) experienced other adverse events that were considered to have a possible or probable relationship to the product. These included chills, phlebitis, vasodilatation, and paresthesia. All adverse events were mild or moderate in intensity.

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. Early reports might indicate a higher incidence in females. Caution should be exercised and antithrombotic measures should be considered in all VWD patients in situations of high thrombotic risk. See **WARNINGS.**

DOSAGE AND ADMINISTRATION

GENERAL - 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 carefully weighed by the physician and discussed with the patient.

Humate-P® is for intravenous administration only.

Each vial of Humate-P® contains the labeled amount of Factor VIII activity in IU for the treatment of hemophilia A. Additionally, each vial of Humate-P® also contains VWF:RCo activity in IU for the treatment of VWD.

THERAPY FOR HEMOPHILIA A - As a general rule, 1 IU of Factor VIII activity per kg body weight will increase the circulating Factor VIII level by approximately 2 IU/dL. Adequacy of treatment must be judged by the clinical effects; thus, the dosage may vary with individual cases. Although dosage must be individualized according to the needs of the patient (weight, severity of hemorrhage, presence of inhibitors), the following general dosages are recommended for adult patients:[20]

Table 4: Dosage recommendations for the treatment of Hemophilia A

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 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 FVIII:C plasma level of approximately 50% of normal, followed by 15 IU FVIII:C/kg every 8 – 12 hours for first 1 – 2 days to maintain FVIII:C plasma level at 30% of normal, and then the same dose once or twice a day for a total of up to 7 days, or until adequate wound healing.
Life-threatening hemorrhage: • Major operations • Gastrointestinal bleeding • Neck, tongue or pharyngeal hematoma with potential for airway compromise • Intracranial, intraabdominal or intrathoracic bleeding • Fractures	Initially 40 to 50 IU FVIII:C/kg, followed by 20 – 25 IU FVIII:C/kg every 8 hours to maintain FVIII:C plasma level at 80–100% of normal for 7 days, then continue the same dose once or twice a day for another 7 days in order to maintain the FVIII:C level at 30–50% of normal.

In all cases, the dose should be adjusted individually by clinical judgement of the potential for compromise of a vital structure, and by frequent monitoring of factor VIII activity in the patient's plasma.

Pediatric Use for Hemophilia A:

See **PRECAUTIONS.**

THERAPY FOR VON WILLEBRAND DISEASE – The dosage should be adjusted according to the extent and location of bleeding. As a rule, 40–80 IU VWF:RCo (corresponding to 16 to 32 IU factor VIII in Humate-P®) per kg body weight are given every 8 to 12 hours. Repeat doses are administered for as long as needed based on repeat monitoring of appropriate clinical and laboratory measures. Expected levels of VWF:RCo are based on an expected *in vivo* recovery of 1.5 IU/dL rise per IU/kg VWF:RCo administered. The administration of 1 IU of Factor VIII per kg body weight can be expected to lead to a rise in circulating VWF:RCo of approximately 3.5 to 4 IU/dL. The following table provides dosing guidelines for pediatric and adult patients.[21]

Table 5: Dosing recommendations for the treatment of von Willebrand Disease

Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg body weight)
Type 1 • mild, if desmopressin is inappropriate (Baseline VWF:RCo activity typically >30%)	Major (e.g. severe or refractory epistaxis, GI bleeding, CNS trauma, or traumatic hemorrhage)	Loading dose 40 to 60 IU/kg, then 40 to 50 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of VWF:RCo >50%; then 40 to 50 IU/kg daily for a total of up to 7 days of treatment.
• moderate or severe (Baseline VWF:RCo activity typically <30%)	Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg (1 or 2 doses)
	Major (e.g. severe or refractory epistaxis, GI bleeding, CNS trauma, hemarthrosis or traumatic hemorrhage)	Loading dose 50 to 75 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of VWF:RCo >50%; then 40 to 60 IU/kg daily for a total of up to 7 days of treatment. Factor VIII:C levels should be monitored and maintained according to the guidelines for hemophilia A therapy, Table 4.
Types 2 (all variants) and 3	Minor (clinical indications above)	40 to 50 IU/kg (1 or 2 doses)
	Major (clinical indications above)	Loading dose of 60 to 80 IU/kg, then 40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of VWF:RCo >50%, then 40 to 60 IU/kg daily for a total of up to 7 days of treatment. Factor VIII:C levels should be monitored and maintained according to the guidelines for hemophilia A therapy, Table 4.

Reconstitution

1. Warm both diluent and Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® in unopened vials to room temperature [not above 37°C (98°F)].
2. Remove caps from both vials to expose central portions of the rubber stoppers.
3. Treat surface of rubber stoppers with the alcohol swab provided and allow to dry.
4. Using aseptic technique, pierce the double needle of the transfer set into the diluent vial. Remove the protective cap and insert the exposed (longer) needle into the upright Humate-P® vial. The diluent will be transferred into the Humate-P® by vacuum.
5. Remove the diluent vial and the transfer set and discard.
6. Gently rotate the vial. DO NOT SHAKE VIAL. Vigorous shaking will prolong the reconstitution time. Continue swirling until the powder is dissolved and the solution is ready for administration. To assure product sterility, Humate-P® should be administered within three hours after reconstitution.
7. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. When the reconstitution procedure is precisely followed, it is not uncommon for a few small flakes or particles to remain. The filter spike provided with Humate-P® should remove those particles and this should not influence dosage calculations.

Administration

INTRAVENOUS INJECTION

Plastic disposable syringes are recommended for administration of Humate-P® solution. The ground glass surface of all-glass syringes tend to adhere protein solutions of this type.

Use sterile technique, for the following steps:

1. Remove the paper cover from the package containing the disposable filter spike. Attach the filter spike to a sterile disposable syringe and take the filter spike out of the package.
2. Remove the protective cap and – without touching the tip of the filter spike – insert the disposable filter spike into the stopper of the Humate-P® vial; inject air.
3. Draw up the solution slowly (when using several syringes leave the filter spike in the vial). Separate the syringe from the filter spike and attach the syringe to an infusion kit or a suitable injection needle. Discard the filter spike.
4. Slowly inject the solution (maximally 4 mL/minute) intravenously with an infusion kit or with a suitable injection needle.

HOW SUPPLIED

Humate-P® is supplied in a single dose vial with a vial of diluent (Sterile Diluent for Humate-P®), a sterile transfer set for reconstitution, a sterile filter spike for withdrawal and alcohol swabs. International unit activity of Factor VIII and VWF:RCo is stated on the carton and label of each vial and supplied as follows:

	FVIII/vial	VWF:RCo/vial	Diluent
NDC 0053-7620-05	250 IU	500 IU	10 mL
NDC 0053-7620-10	500 IU	1000 IU	20 mL
NDC 0053-7620-20	1000 IU	2000 IU	30 mL

STORAGE

When stored at refrigerator temperature, 2–8°C (36–46°F), Humate-P® is stable for the period indicated by the expiration date on its label. Within this period, Humate-P® may be stored at room temperature not to exceed 30°C (86°F), for up to six months. Avoid freezing, which may damage the diluent container.

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