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 0.2 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 40 to 80 IU Factor VIII activity, 72 to 224 IU VWF:RCo activity[1], 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 30 mg of total proteins.

This product is prepared from pooled human plasma collected from U.S. licensed facilities in the U.S. All Source Plasma used in the manufacture of this product was tested by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1 and found to be nonreactive (negative).

An investigational NAT for HBV was also performed on all Source Plasma used in the manufacture of this product and found to be nonreactive (negative). The aim of the HBV test is to detect low levels of viral material, however, the significance of a nonreactive (negative) result has not been established.

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**).

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, Laboratory Tests**).

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 Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, 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 subjects 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, 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 subjects 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 subjects, 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 subjects and in most cases this improvement was sustained through 22 to 26 hours postinfusion.

[1] This correlates to a VWF:RCo to Factor VIII activity average ratio of 2.4 which is used to calculate the nominal values of VWF:RCo activity and is the average VWF:RCo activity.

Pharmacokinetics were also evaluated in 28 subjects in a European study in the nonbleeding state prior to a surgical procedure. The median half-life of VWF:RCo was 6.3 hours (range: 1.1 to 14.1 hours). The median *in vivo* recovery for VWF:RCo activity was 1.9 IU/dL per IU/kg (range: 0.6 to 4.5). Infusion of AHF/VWF complex corrected the defect of the multimer pattern in subjects with types 2A and 3 VWD. Large multimers were detectable until at least 8 hours after infusion.

Clinical Studies

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 were provided with product under an Emergency Drug Release Program. Dosage schedule and duration of therapy were determined by the judgment of the medical practitioner.

There were 514 requests for product use for surgery, bleeding or prophylaxis in the 97 Canadian subjects. 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 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. 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 subjects 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 subjects. In type 3 subjects, 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 Subjects

	Diagnosis							
	Type 1 VWD		Type 2A VWD		Type 2B VWD		Type 3 VWD	
NUMBER OF SUBJECTS	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 subjects a summary of the number of subjects 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 Subjects

	Diagnosis							
	Type 1 VWD		Type 2A VWD		Type 2B VWD		Type 3 VWD	
NUMBER OF SUBJECTS	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 subjects) 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 Subjects		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	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 Subjects	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	0.1
Day 2	No. of Subjects	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 Subjects	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)

A European clinical trial investigated the safety and hemostatic efficacy of VWF/AHF in subjects with VWD undergoing surgery. This trial did not have a pre-stated hypothesis to evaluate hemostatic efficacy. A total of twenty-seven (27) subjects (18 females and nine males) with VWD underwent surgical procedures. The ages of these subjects ranged from 5 to 81 years old (median 46); two were 16 years old or younger, and five were above 65 years old. Ten subjects had type 1 VWD, nine had type 2A, one had type 2M, and seven had type 3. Sixteen (16) of the surgical procedures were classified as major (orthopedic joint replacement, hysterectomy, multiple tooth extractions, laparoscopic adnexectomy, laparoscopic cholecystectomy, and basal cell carcinoma excision). Hemostatic efficacy as assessed by the investigator at the end of the study (Day 14) was either excellent or good in all cases. In one subject with type 3 VWD, the investigator's assessment of efficacy immediately after surgery was moderate, but was excellent/good for all subsequent assessments.

Viral Safety

Clinical evidence of the viral safety of Humate-P® was obtained in additional studies. In one study, all evaluable subjects (31 of 67) who received Humate-P® remained HBs-antigen negative. None of the 31 subjects 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 subjects 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 subjects 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 subject developed any signs of an infectious disease.[15]

In a retrospective study, all 155 subjects 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 subjects were also tested for HIV-2 antibodies and all remained seronegative.[16]

INDICATIONS AND USAGE

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, 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 with von Willebrand disease for treatment of spontaneous and trauma-induced bleeding episodes. This applies to patients with severe VWD as well as patients with mild to moderate VWD 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 have not been evaluated in VWD subjects. Adequate data are not presently available on which to evaluate or to base dosing recommendations in this setting. A clinical trial to evaluate efficacy and safety of prophylactic dosing with Humate-P® in VWD subjects requiring elective surgery and to provide dosing recommendations in this setting is ongoing in the US.

CONTRAINDICATIONS

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® is contraindicated in individuals with a history of anaphylactic or severe systemic response to antihemophilic factor or von Willebrand factor preparations. It is also contraindicated in individuals with a known hypersensitivity to any of its components.

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**.

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Humate-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 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 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 60ºC 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.

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 after use.

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.

Laboratory Tests

Antihemophilic Factor/von Willebrand Factor (Human), Dried, Pasteurized, Humate-P® 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 Factor VIII levels of VWD patients receiving Humate-P® should be monitored using standard coagulation tests, especially in cases of surgery.

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 subjects. 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 subjects, including infants, children and adolescents but has not yet been evaluated in neonates. The safety of Humate-P® for the prevention of excessive bleeding during and after surgery was demonstrated in 7 pediatric subjects (ages 2-15) with VWD. 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

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**). 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. In some cases, inhibitors to coagulation factors may occur. However, no inhibitor formation was observed in any of the clinical trials.

Although few adverse reactions have been reported in patients receiving Humate-P® for treatment of hemophilia A and VWD, the most commonly reported are allergic-anaphylactic reactions (including urticaria, chest tightness, rash, pruritus, edema, and shock). For patients undergoing surgery, the most common adverse reactions are postoperative wound or injection-site bleeding.

Adverse Reactions in Clinical Trials

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.

von Willebrand Disease

Treatment of 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. Four of 97 (4%) subjects experienced seven adverse events that were considered to have a possible or probable relationship to the product. These included chills, phlebitis, vasodilatation, 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 mild vasodilatation (1/9), allergic reactions (2/9), pruritus (1/9), and paresthesia (2/9); moderate peripheral edema (1/9) and extremity pain (1/9); and severe pseudothrombocytopenia (platelet clumping with a false low reading) (1/9). Humate-P® was discontinued in the subject who experienced the peripheral edema and extremity pain.

VWD Subjects Undergoing Surgery

Among the 46 VWD subjects who received Humate-P® for prevention of excessive bleeding during and after surgery, including 1 subject who underwent colonoscopy without the planned polypectomy, the most common adverse events were postoperative hemorrhage (22 events in 13 subjects with two subjects experiencing bleeding at up to 3 different sites), and postoperative nausea and pain, each in 7 subjects. Postoperative hemorrhagic adverse events are shown in Table 4.

Table 4: Hemorrhagic Adverse Events in 46 Surgical Subjects

Adverse Event	Surgical Procedure Category	N subjects/events	Onset*		Severity		
			On	Post	Mild	Mod	Severe
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
Wound/injection site bleeding	Major	5/8	5	3	6	–	2
	Major	2/2	1	1	1	1	–
Menorrhagia	Major	1/1	1+	–	–	1	–
Groin bleed	Oral	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 after intracranial surgery

§ Two of these events reported as serious adverse events occurring after gastrojejunal bypass

\+ Reported as serious adverse event after hysteroscopy and dilatation and curettage

One additional subject whose pre-operative blood hemoglobin value was 8.7 g/dL was transfused with red cells after the subject's post-operative hemoglobin value had decreased to 7.6 g/dL. This subject's intraoperative blood loss had been estimated at <5 mL

Table 5 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 that was considered possibly related to Humate-P® occurred in one elderly subject who underwent bilateral knee replacement.

Table 5: Non-Hemorrhagic and Possibly Related Adverse Events in 46 Surgical Subjects

Body System	Adverse Event	Number of Subjects with an AE Not Related to Humate-P®*	Number of Subjects with an AE Possibly Related to Humate-P®	Total Number of Subjects with an AE Regardless of Causality
Body as a whole	Pain	7	–	7
	Fever	3	–	3
	Infection	3	–	3
	Surgery	3	–	3
	Facial Edema	2	–	2
Cardiovascular	Chest Pain	2	–	2
	Pulmonary embolus#	–	1	1
	Thrombophlebitis#	–	1	1
Digestive	Nausea	6	1	7
	Constipation	3	–	3
	Vomiting	–	1	1
Hemic and Lymphatic System	Anemia / Decreased hemoglobin	2	–	2
Metabolic/Nutritional	Increased SGPT	–	1	1
Nervous	Headache	3	1	4
	Dizziness	1	1	2
	Insomnia	2	–	2
	Increased sweating	2	–	2
Skin and Appendages	Pruritus	2	–	2
	Rash	–	1	1
Urogenital	Urinary tract infection	2	–	2

* Occurring in two or more subjects

\# These events occurred in separate subjects

Seven subjects experienced eight post-operative serious adverse events: one with subdural hematoma and intracerebral bleeding following intracranial surgery related to an underlying cerebrovascular abnormality: and one each with gastrointestinal bleeding following gastrojejunal bypass, sepsis, facial edema, infection, menorrhagia following hysteroscopy and dilatation and curettage, and pulmonary embolus.

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 frequency 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 Factor VIII, and hemolysis. Additional adverse reactions reported for VWD are thromboembolic complications, chills and fever, and hypervolemia.

Evaluation and interpretation of these postmarketing events is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

Healthcare professionals should report serious adverse events possibly associated with the use of Humate-P® to ZLB Behring at 1-800-504-5434 or FDA's MedWatch reporting system at 1-800-FDA-1088.

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.

Antihemophilic Factor/von Willebrand (Human), Dried, Pasteurized, 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 6: 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 17 to 33 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 7: 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.
	Minor (e.g. epistaxis, oral bleeding, menorrhagia)	40 to 50 IU/kg (1 or 2 doses)
· moderate or severe (Baseline VWF:RCo activity typically <30%)	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 6.
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 6.

Reconstitution
1. Warm both diluent and 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 tends 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

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, 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 listed below. Note: Use either the double-ended needle and vented filter spike provided or the commercially available transfer device manufactured by Medimop Medical Projects Ltd., Mix2Vial™* (15 micron) order number 7970-20 for reconstitution and withdrawal. *Approved for both reconstitution and withdrawal under 510(k).

	FVIII/vial	VWF:RCo/vial	Diluent
NDC 0053-7615-05	250 IU	600 IU	5 mL
NDC 0053-7615-10	500 IU	1200 IU	10 mL
NDC 0053-7615-20	1000 IU	2400 IU	15 mL

STORAGE

When stored at refrigerator temperature, 2-8°C (36-46°F), Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, 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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