PRODUCT MONOGRAPH

HUMATE-P®

Antihemophilic Factor / von Willebrand Factor Complex (Human), Dried, Pasteurized

(200-300) IU* / (360-840) IU*, reconstituted with 5 mL diluent
(400-600) IU* / (720-1680) IU*, reconstituted with 10mL diluent
(810-1200) IU* / (1440-3360) IU*, reconstituted with 15 mL diluent

Coagulation Factor
(ATC Classification Code: B02BD05)

CSL Behring Canada, Inc.
55 Metcalfe Street, Suite 1460
Ottawa, Ontario
K1P 6L5

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*An international unit (IU) is defined by current international standards. One IU Factor VIII or 1 IU vWF:RCof is approximately equal to the level of Factor VIII or vWF:RCof found in 1.0 mL of fresh-pooled plasma.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Injection	Factor VIII / von Willebrand Factor Activity 250 / 600 IU/Vial 500 / 1200 IU/Vial 1000 / 2400 IU/Vial Dried, pasteurized preparation to be reconstituted with diluent prior to injection.	Glycine, Albumin (Human), Sodium chloride and Sodium citrate. *For a complete listing see **Dosage Forms, Composition and Packaging** section.*

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) for intravenous administration in the treatment of patients with classical hemophilia (hemophilia A) and von Willebrand disease (VWD).

INDICATIONS AND CLINICAL USE

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), (2) in adult and pediatric patients (see **WARNINGS AND PRECAUTIONS** section, subsection **Pediatrics**) 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 and (3) to prevent excessive bleeding (i.e. bleeding that exceeds the expected blood loss under a given condition) during and after surgery in adult and pediatric patients.

CONTRAINDICATIONS

None known, caution is advised in patients with a known allergic reaction to constituents of the preparation.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Serious thromboembolic events have been reported in patients with von Willebrand disease who are treated with coagulation factor replacement therapy (see **Cardiovascular** section below).
- May potentially contain infectious agents (see **General** section below).

General

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.

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® is made from human plasma. Products made from large pools of human plasma may contain infectious agents, including the causative agents of hepatitis and other 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 **PART II, PHARMACEUTICAL INFORMATION** section, **Viral Inactivation**). 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 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.

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 and may induce red cell aplasia in some of these patients.

Although the overwhelming numbers 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.

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. 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 1-613-783-1892. The physician should discuss the risks and benefits of this product with the patient.

Patients who are undergoing treatment using a therapeutic product derived from human blood or plasma should be appropriately vaccinated.

Other precautions are as follows:

- The administration equipment and any unused Humate-P® should be discarded.

Cardiovascular

Serious thrombotic/thromboembolic events including pulmonary embolism have been reported in VWD patients receiving coagulation factor replacement therapy, especially in the setting of known risk factors for thrombosis (e.g. perioperative periods without thromboprophylaxis, immobilization, obesity, overdose and cancer). In these patients caution should be exercised and antithrombotic measures and FVIII monitoring should be considered.[1, 2, 3]

Hematologic

This Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, 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.

Special Populations

Pregnant Women:

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 and the expected benefit outweighs any potential risk.

Pediatrics:

Hemophilia A

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.

Von Willebrand Disease

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. The safety of Humate-P® for the prevention of excessive bleeding during and after a surgery was demonstrated in 8 pediatric subjects (age 3-15) with VWD. Of the 34 pediatric studied for both treatment of von Willebrand disease and prevention of excessive bleeding during and after surgery, 4 were infants (1 month old to under 2 years of age), 23 were children (2 through 12 years old), and 7 were adolescents (13 through 15 years old). As in adults, pediatric patients should be dosed based upon body weight (kg) in accordance to information in the **DOSAGE AND ADMINISTRATION** section.

Monitoring and Laboratory Tests

Strong consideration should be given to monitoring vWF:RCof and F-VIII levels in VWD patients receiving Humate-P® for the prevention of excessive bleeding during and after surgery. It is advisable to monitor trough vWF:RCof and FVIII:C levels at least once daily in order to adjust the dosage of Humate-P® as needed, to avoid excessive accumulation of coagulation factors.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized Humate-P® is usually tolerated without reaction. 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 or VWF may occur.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

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.

In a study of 71 VWD patients, the safety of Humate-P® was evaluated in 53 serious bleeding events and 42 surgical events. Nine (9/95, 9.5%) adverse events were considered to have a possible or probable relationship to the product and included mild allergic reaction, paresthesia, vasodilatation, peripheral edema, extremity pain, pseudo-thrombocytopenia and pruritus. Seven (7/95, 7.4%) serious adverse events were considered non-related and included menorrhagia, anemia, hemorrhage, abdominal pain, infection, abnormal wound healing and pneumonia.

VWD Subjects Undergoing Surgery

Among 63 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 bleeding (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). Postoperative bleeding adverse events are shown in **Table 1**. Although these events were not considered by the investigators as the result of ineffective hemostasis, the lack of efficacy due to inadequate dosing or duration of treatment is a possible risk factor. Even though dosage values are given in the section DOSAGE AND ADMINISTRATION, the clinical effect of Humate-P® remains the single most important factor to determine adequacy of treatment, thus the dosage should be adjusted as needed.

Table 1: Bleeding Adverse Events in 63 Surgical Subjects

Adverse Events	**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 after intracranial surgery.

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

[+] Reported as serious adverse events requiring hysterectomy after hysteroscopy and dilation and curettage.

Table 2 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®. A pulmonary embolus that was considered possibly related to Humate-P® occurred in one elderly subject who underwent bilateral knee replacement.

Table 2: Non-Hemorrhagic and Possibly Related Adverse Events (AE) in 63 Surgical Subjects

Body System	Adverse Event	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	Increase SGPT	1	1
Nervous	Dizziness	1	5
	Headache	1	4
	Increase Sweating	-	3
	Insomnia	-	2
Skin and Appendages	Pruritus	-	3
	Rash	1	1
Urogenital	Urinary Retention	-	4
	Urinary Tract Infection	-	2

* Occuring in two or more subjects.
[#] These events occurred in separate subjects.

Eight subjects experienced 10 post-operative 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 hysteroscopy and dilatation and curettage, pyelonephritis, and pulmonary embolus.

Post-Market Adverse Drug Reactions

The following adverse reactions are based on post-marketing experience. The following standard categories of frequency are used:

Very common	≥	1/10
Common	≥	1/100 and < 1/10
Uncommon	≥	1/1,000 and < 1/100
Rare	≥	1/10,000 and < 1/1,000
Very rare	<	1/10,000
Unknown		Frequency cannot be estimated from the available data.

Table 3: Postmarket Adverse Drug Reactions

MedDRA SOC	Adverse Reaction	Frequency
Blood and Lymphatic System Disorders	Hypervolemia Haemolysis VWF inhibition FVIII inhibition	Unknown Unknown Very rare Very rare
General Disorders and Administration Site Conditions	Fever	Very rare
Immune System Disorders	Hypersensitivity (allergic reactions)	Very rare
Vascular Disorders	Thrombosis Thromboembolic events Pulmonary embolism events	Very rare Very rare

DRUG INTERACTIONS

There are no known interactions of Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® with other agents.

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.

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:RCof activity in IU for the treatment of VWD.

Recommended Dose and Dosage Adjustment

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[4]:

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 judgment 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 **WARNINGS AND PRECAUTIONS** section.

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:RCof 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:RCof are based on an expected *in vivo* recovery of 2.0 IU/dL rise per IU/kg vWF:RCof administered. The administration of 1 IU of Factor VIII per kg body weight can be expected to lead to a rise in circulating vWF:RCof of approximately 5 IU/dL. The following table provides dosing guidelines for pediatric and adult patients.[5]

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

Classification of VWD	Hemorrhage	Dosage (IU vWF:RCof /kg body weight)
Type 1 • mild, if desmopressin is inappropriate (Baseline vWF:RCof activity typically >30%)	Major (e.g. severe or refractory epistaxis, GI bleeding, CNS trauma, or traumatic hemorrhage)	40 to 50 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of vWF:RCof >50%; then 40 to 50 IU/kg daily for a total of up to 7 days of treatment.
• moderate or severe (Baseline vWF:RCof 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)	40 to 60 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of vWF:RCof >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)	40 to 80 IU/kg every 8 to 12 hours for 3 days to keep the nadir level of vWF:RCof >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.

For additional information, see the *Clinical Practice Guidelines; Hemophilia and von Willebrand disease; 2. Management* by the Association of Hemophilia Clinic Directors of Canada, Edition 2, Update 2, July 7, 1999.

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 IU/kg and, subsequently, closely monitor the patient's through coagulation factor levels.

When possible, it is recommended that the incremental *in vivo* recovery (IVR) be measured and that baseline plasma vWF:RCof and FVIII:C be assessed in all patients prior a surgery. Measure IVR as follows:

1. Measure baseline plasma vWF:RCof.
2. Infuse 60 IU vWF:RCof/kg b.w. intravenously at time 0.
3. At time +30 minutes, measure plasma vWF:RCof.

$$IVR = (\text{plasma vWF:RCof}_{\text{time + 30 min}} - \text{plasma vWF:RCof}_{\text{baseline}}) / 60 \text{ IU/kg}$$

Calculation of the loading dose requires four values: the target peak plasma vWF:RCof level, the baseline vWF:RCof level, body weight (bw) in kilograms, and IVR. When individual values are not available (e.g. in the case of emergency surgery), a standardized loading dose can be used based on an assumed vWF:RCof IVR of 2.0 IU/dL per IU/kg of vWF:RCof product administered. **Table 6** provides dosing guidelines for adults and pediatric patients.

Table 6: vWF:RCof and FVIII:C Loading Dose Recommendations for the Prevention of Excessive Bleeding During and After Surgery

Type of Surgery	vWF:RCof 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:RCof x BW (kg) / IVR# = IU vWF:RCof required If the incremental IVR is not available (e.g. in the case of emergency surgery), assume an IVR of 2 IU/dL per IU/kg and calculate the loading dose as follows: (100 – baseline plasma vWF:RCof) x BW (in kg) / 2.0
Minor / oral §	50-60 IU/dL	40-50 IU/dL	Δ* vWF:RCof x BW (kg) / IVR#= IU vWF:RCof required

* Δ = Target peak plasma vWF:RCof-baseline plasma vWF:Rcof.
# IVR= Incremental recovery as measured in the patient.
§ Oral surgery is defined as removal of fewer than three teeth, if the teeth are non-molars and have no bony involvement. Removal 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. Removal 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:RCof level of 100 IU/dL, baseline vWF:RCof level 20 IU/dL, an IVR of 2.0 (IU/dL)/(IU/kg), Δ of 80 IU/dL, and a body weight of 70 kg would be calculated as follows:

(80 IU/dL x 70 kg) / 2 (IU/dL)/(IU/kg) = 2,800 IU vWF:RCof required

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

The initial maintenance dose for the prevention of excessive bleeding during and after surgery should be half the loading dose, irrespective of additional dosing required to meet FVIII:C targets. **Table 7** provides recommendations for target through plasma levels (based on the type of surgery and the number of days following surgery) and minimum duration of treatment for subsequent maintenance doses. These recommendations apply to both adult and pediatric patients.

Based on individual pharmacokinetic-derived half-lives, the frequency of maintenance doses is generally every 8 to 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.

Table 7: vWF:RCof and FVIII:C Target Through 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:RCof Target Trough Plasma Levels*		FVIII:C Target Trough Plasma Levels*		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[§]

*Trough levels for either coagulation factor should not exceed 100 IU/dL.

[#]Oral surgery is defined as removal of fewer than three teeth, if the teeth are non-molars and have no bony involvement. Removal 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. Removal of more than two teeth is considered major surgery in all patients.

[§]At least one maintenance dose following surgery based on individual pharmacokinetic values.

It is advisable to monitor trough vWF:RCof and FVIII:C levels at least once daily in order to adjust Humate-P® dosing as needed to avoid excessive accumulation of coagulation factors. The duration of the treatment generally depends on the type of surgery performed, but must be assessed for individual patients based on their hemostatic response (see **CLINICAL TRIALS section**).

For use in pediatric VWD patients, see **PRECAUTIONS section, use in Pediatric.**

Administration

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® is for INTRAVENOUS ADMINISTRATION only.

Prepare and administer using aseptic techniques.

To assure product sterility, Humate-P® should be administered within 3 hours after reconstitution.

Slowly inject the solution (maximally 4 mL/minute) intravenously with a venipuncture set or with another suitable injection set.

Discard the administration equipment and any unused Humate-P® after use.

Reconstitution:

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

1. Before infusion ensure that Humate-P® and diluent vial are at room temperature.

2. Remove the Humate-P® and diluent vial flip caps to expose central portions of the rubber stoppers.

3. Wipe the rubber stoppers with an antiseptic solution such as an alcohol swab and allow to dry prior to opening the Mix2Vial™ package.

4. Open the Mix2Vial™ package by peeling away the lid (Fig. 1). To maintain sterility, leave the Mix2Vial™ in the clear outer packaging. Place the diluent vial on an even surface and hold the vial tight. Grip the Mix2Vial™ together with the clear packaging and firmly snap the blue end onto the diluent stopper (Fig. 2).

5. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial™ set. Make sure that you only pull up the clear outer packaging and not the Mix2Vial™ set (Fig. 3).

6. With the product vial firmly on a surface, invert the diluent vial with set attached and firmly snap the transparent adapter onto the product vial stopper (Fig. 4). The diluent will automatically transfer into the product vial.

7. With the diluent and product vial still attached, gently swirl the product vial to ensure the product is fully dissolved (Fig. 5). Do not shake vial.

8. With one hand grasp the product-side of the Mix2Vial™ set and with the other hand grasp the blue diluent-side of the Mix2Vial™ set and unscrew the set into two pieces (Fig. 6).

9. Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial™ set. Inject air into the product 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).

10. 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™ (Fig. 8). Attach the syringe to a venipuncture set.

11. If the same patient is to receive concentrate from more than one vial, the contents of two vials may be drawn into the same syringe through a separate unused Mix2Vial™ set before attaching the vein needle.

12. 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 after reconstitution. To assure product sterility, Humate-P® should be administered within three hours after reconstitution.

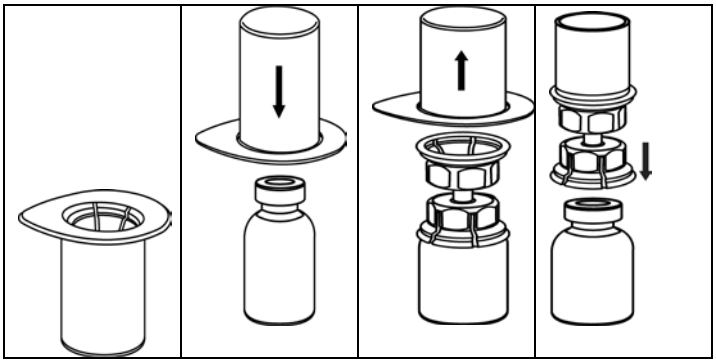

Fig. 1 Fig. 2 Fig. 3 Fig. 4

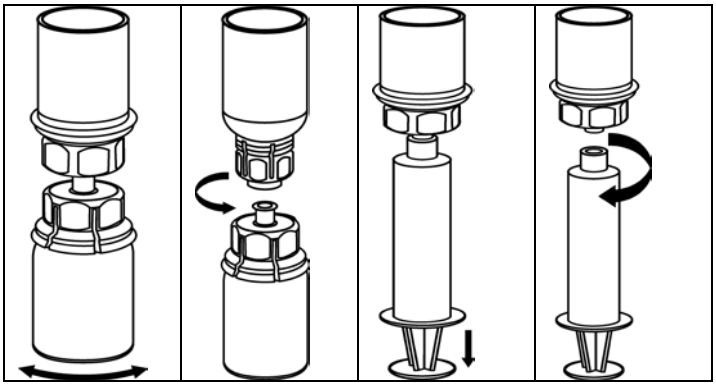

Fig. 5 Fig. 6 Fig. 7 Fig. 8

OVERDOSAGE

No symptoms of overdose with Antihemophilic Factor/von Willebrand Factor Complex, (Human), Dried, Pasteurized, Humate-P® are known so far.

ACTION AND CLINICAL PHARMACOLOGY

Hemophilia A is a hereditary disorder of blood coagulation associated with a deficiency of antihemophilic factor VIII activity. It manifests most frequently in males and results in bleeding into joints, muscles or internal organs. Female carriers may also be at risk with surgery.

Factor VIII is essential to the intrinsic pathway of blood coagulation in the activation of factor X, ultimately leading to the conversion of prothrombin to thrombin, thus maintaining effective haemostasis.

VWD is caused by quantitative or qualitative abnormalities of the vWF, a protein present in plasma and platelets in the form of multimers of which the high molecular weight multimers support platelet adhesion to the subendothelium.[6]

Pharmacodynamics

In severe forms of VWD and in these forms where the vWF is qualitatively abnormal (e.g. type II VWD), the use of plasma-derived products is a prerequisite for normalization of the bleeding time. Humate-P® has been shown to contain vWF with a multimeric pattern similar to that of normal plasma.[7, 8, 9] When administered to patients with VWD [types 1, 2 (A,B,C), 3][8, 10, 11, 12, 13, 14, 15] effective haemostasis was achieved, as evidenced by decreased bleeding time. This effect was correlated with the presence of a multimeric composition of vWF similar to that found in normal plasma.[8, 10]

Pharmacokinetics

Pharmacokinetics in Hemophilia A

After intravenous injection of Humate-P in humans, there is a rapid increase in the plasma level of antihemophilic factor followed by a rapid decrease in activity (time of equilibration with the extravascular compartment) and a subsequent slower rate of decrease in activity (biological half-life). Studies with Humate-P® in hemophilic patients have demonstrated a mean initial half-disappearance time of 8 hours and a mean biological half-life of 12.2 hours (range: 8.4 to 17.4 hours).[16]

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.[7-8, 17-19]

When administered to patients with VWD (types 1, 2 [A, B, C], or 3)[20], bleeding time decreased.[8, 10, 11, 19, 21] This effect was correlated with the presence of a multimeric composition of vWF similar to that found in normal plasma.[8, 10, 11, 18, 19]

Pharmacokinetic studies of Humate-P® have been performed with cohorts of subjects in the non-bleeding state. Wide inter-subject variability was observed in pharmacokinetic values obtained from these studies.
The pharmacokinetics of Humate-P® were evaluated in 41 subjects in a prospective US study in the non-bleeding state prior to a surgical procedure. Subjects received 60 IU vWF:RCof/kg body weight of Humate-P®. Sixteen subjects had type 1 VWD, two had type 2A, four had type 2B, six had type 2M, and 13 had type 3. The median terminal half-life of vWF:RCof was 11 hours

(range: 3.5 to 33.6 hours), excluding five subjects with a half-life exceeding the blood sampling time of 24 or 48 hours. The median clearance and volume of distribution at steady sate were 3.1 mL/hr/kg (range 1 to 16.6 mL/hr/kg) and 53 mL/kg (range 29 to 141 mL/kg), respectively. The median *in vivo* recovery for vWF:RCof activity was 2.4 IU/dL per IU/kg (range: 1.1 to 4.2). High molecular weight multimers 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®.

Pharmacokinetics were also evaluated in 28 subjects in a European study in the non-bleeding state prior to a surgical procedure. Subjects received 80 IU vWF:RCof/kg body weight of Humate-P®. Ten subjects had type 1 VWD, 10 had type 2A, one had type 2M, and seven had type 3. The median terminal half-life of vWF:RCof was 10 hours (range: 2.8 to 28.3 hours) excluding one subject with a half-life exceeding the blood sampling time of 48 hours. The median clearance and volume of distribution at steady state were 4.8 mL/hr/kg (range: 2.1 to 53 mL/hr/kg) and 59 mL/kg (range: 32 to 290 mL/kg), respectively. The median *in vivo* recovery for vWF:RCof activity was 1.9 IU/dL per IU/kg (range: 0.6 to 4.5). 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 types of VWD have no impact on the pharmacokinetics of vWF:RCof.

STORAGE AND STABILITY

When stored at room temperature, up to 25°C, Humate-P® is stable for the period indicated by the expiration date on its label. Avoid freezing, which may damage the diluent container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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:RCof) activity expressed in international unit (IU) (see **DOSAGE AND ADMINISTRATION section**). An IU is defined by current international standards. One IU Factor VIII or 1 IU vWF:RCof is approximately equal to the level of Factor VIII or vWF:RCof found in 1.0 mL of fresh-pooled human plasma.

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

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® is supplied in a single-use vial with a vial of diluent containing sterile water for injection(meets USP chemistry requirements for Sterile Water for Injection, except for pH; pH 4.5-8.5), Mix2Vial™, a needleless filter transfer device for reconstitution and withdrawal of the product. International unit activity of Factor VIII and vWF:RCof is stated on the carton and label of each vial.

The reconstituted preparations have the following antihemophilic factor and vWF:RCof activity per mL:

Vial size (IU/vial) (F VIII:C/ vWF:RCof)	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration (IU/mL) (F VIII:C/vWF:RCof)
250/600	5 mL	5 mL	50 / 120
500/1200	10 mL	10 mL	50 / 120
1000/2400	15 mL	15 mL	67 / 160

Upon reconstitution with the volume of diluent provided [Diluent (sterile water for injection)], each mL of Humate-P® contains 40 to 80 IU Factor VIII activity, 72 to 224 IU vWF:RCof activity, 8 to 16 mg of Albumin (Human), 15 to 33 mg of glycine, 2 to 5.3 mg of sodium chloride, <0.1 µg aluminum, 3.5 to 9.3 mg of sodium citrate, 2 to 14 mg of other proteins, and 10 to 20 mg of total proteins. Humate-P® contains no preservative.

To assure product sterility, Humate-P® should be administered within 3 hours after reconstitution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Antihemophilic Factor and von Willebrand Factor complex
Molecular formula and molecular mass:	Antihemophilic Factor: 170 to 280 kDa vWF multimers: 500 to 20,000 kDa

Physicochemical properties

Physical state:	Liquid solution
Appearance:	Colorless and clear to slightly opalescent solution

Composition:

The following composition is adjusted by dissolution of the 2nd sodium chloride precipitate, dialysis and dilution to obtain the final bulk.

Table 8: Composition

	Target 250/500 IU	**Specifications 250/500 IU***	**Target 1000 IU**	**Specifications 1000 IU***
F VIII (Q-10-001)	53-57 IU/mL	40-60 IU/mL	53-57 IU/mL	54-80 IU/mL
vWF:RCoF (Q-10-122)		72-168 IU/mL		96-224 IU/mL
vWF:Ag (Q-04-035)		90-220 IU/mL		130-300 IU/mL
Glycine (Q-16-204)	20 mg/mL	15-25 mg/mL	26.7 mg/mL	20-33 mg/mL
Sodium chloride (Q-16-334)	3 mg/mL	2-4 mg/mL	4 mg/mL	2.7-5.3 mg/mL
Tri-sodium citrate (Q-16-048)	5.5 mg/mL	3.5-7.0 mg/mL	7 mg/mL	4.7-9.3 mg/mL
Human Serum Albumin (Q-04-031)	10 mg/mL	8-12 mg/mL	13.3 mg/mL	10.6-16.0 mg/mL
pH (Q-10-024)	7.0	6.8-7.4	7.0	6.8-7.4
Osmolality (Q-16-023)		350-550 mosmol/kg		450-700 mosmol/kg

*Drug Product specifications.

Product Characteristics

The active ingredient of Humate-P® is Antihemophilic Factor and von Willebrand Factor Complex, which is derived from human plasma. Factor VIII is synthesized in liver cells as a large single-chain glycoprotein of approximately 300 kDa containing three domains A, B and C arranged in the order A1 : A2 : B : A3 : C1 : C2.[22-24] Shortly after synthesis FVIII is cleaved to form a heterodimer consisting of an 80 kDa light chain (domains A3 : C1 : C2) and a heavy chain of a variable size ranging from 90 to approximately 200 kDa (domains A1 : A2 and a variable amount of B domain).[23-26] The binding sites for vWF are localized in the light chain of factor VIII.[27]

The vWF is synthesized in megakaryocytes and endothelial cells and circulates in plasma in the form of multimers with a size ranging from 500 to approximately 20,000 kDa. The vWF is synthesized as a 260 kDa precursor (pro-vWF) that takes the form of a dimer intracellularly. The dimers undergo glycosylation before they are released into the plasma where a further transformation into multimers occurs.[28-32]

Viral Inactivation

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.

To assure product sterility, Humate-P® should be administered within 3 hours after reconstitution.

The manufacturing procedure for Humate-P® includes multiple processing steps that reduce the risk of virus transmission. The virus reduction capacity of the manufacturing process was evaluated in a series of *in vitro* spiking experiments. The steps evaluated were 1) cryoprecipitation; 2) $Al(OH)_3$ adsorption, glycine precipitation, and NaCl precipitation studied in combination; 3) pasteurization in aqueous solution at 60ºC for 10 hours; and 4) NaCl / glycine precipitation. Total cumulative virus reductions ranged from 7.3 to $\geq$ 13.0 Log_{10} as shown in **Table 9**.

Table 9: Mean Viral Inactivation Factors

Virus Studied	Cryo-precipitation (n)[a] [Log_{10} ± SD]	$Al(OH)_3$ adsorption / glycine precipitation / NaCl precipitation (n)[a] [Log_{10} ± SD]	Pasteurization (n)[a] [Log_{10} ± SD]	NaCl / glycine precipitation (n)[a] [Log_{10} ± SD]	Lyo-philisation (n)[a] [log_{10} ± SD]	Overall Virus Reduction [Log_{10} ± SD]*
	Enveloped Viruses					
HIV	*N.D.*	3.8 ± 0.2 (5)	≥ 6.4 (6)	2.01 ± 0.4 (5)	*N.D.*	≥ 12.2
BVDV	*N.D.*	2.8 ± 0.4 (5)	≥ 8.9 (10)	1.3 ± 0.2 (5)	*N.D.*	≥ 13.0
PRV	1.6±0.3 (2)	3.9 ± 0.6 (7)	4.7 ± 0.4 (10)	1.6 ± 0.3 (5)	*N.D.*	11.8 ± 0.7
WNV[b]	*N.D.*	*N.D.*	≥ 7.8	*N.D.*	*N.D.*	*N.A.*
	Non-Enveloped Viruses					
HAV		2.3 ± 0.3 (6)	4.2 ± 0.4 (6)	1.1 ± 0.3 (5)	1.3 ± 0.2 (14)	8.9 ± 0.6
CPV	1.9 ± 0.5 (7)	3.0 ± 0.4 (5)	1.1 ± 0.2 (9)	1.3 ± 0.4 *(5)*	*N.D.*	7.3 ± 0.8
B19V[c]	*N.D.*	*N.D.*	≥ 3.9	*N.D.*	*N.D.*	*N.A.*

N.D. : Not determined; *N.A.*: Not available.
HIV : Human immunodeficiency virus
BVDV: Bovine diarrhea virus, model for HCV and WNV.
PRV : Pseudorabies virus, model for large enveloped DNA viruses (e.g. herpes virus).
WNV : West Nile virus.
HAV : Hepatitis A virus.
CPV : Canine parvovirus, model for parvovirus B19.
B19V : Parvovoirus B19.
[a]. number of experiments covering production conditions used for evaluation.
[b]. Report: VVSR-WNV-Inactivation 02.
[c]. Report: VER-B19-03.
[*] Calculation of SD only applicable when for all individual factors a Standard Deviation could be calculated.

CLINICAL TRIALS

Study demographics and trial design

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 judgment of the medical practitioner.

Humate-P® was administered to 97 patients, in 530 treatment episodes: 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.

Two 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. In both studies, a pharmacokinetic assessment was performed before a surgical procedure in order to individualize the dosing.

The US clinical study investigated the safety and hemostatic efficacy of Humate-P® in 35 subjects (21 females and 14 males) with VWD undergoing surgery. Subjects ranged from 3 to 75 years old (mean 32.9); seven were 15 years old or younger, and two were 65 years old or older. Twelve 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[a]. 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:RCof level of 100 IU/dL as determined by each subject's calculated *in vivo* recovery (IVR) and baseline vWF:RCof levels); 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:RCof levels of 80 to 100 IU/dL for major surgery and 50 to 60 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:RCof: subsequent maintenance doses were adjusted based on regular measurements of through vWF:RCof 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.

[a]Oral surgery is defined as removal of fewer than three teeth, if the teeth are non-molars and have no bony involvement. Removal 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. Removal of more than two teeth is considered major surgery in all patients.

The European clinical study also investigated the safety and hemostatic efficacy of Humate-P® in 27 subjects (18 females and nine males) with VWD undergoing surgery. This study did not have a pre-stated hypothesis to evaluate hemostatic efficacy. The ages of these subjects ranged from 5 to 81 years old (median 46); one was 5 years old, 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 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.

Clinical evidence of the viral safety of Humate-P® was obtained in additional studies. One study was carried on 67 patients, of which 31 were deemed evaluable for viral safety. In an additional study, a cohort of 26 hemophilic or VWD patients, who had not previously received any blood products, were administered a total of 32 lots of Humate-P®. Markers for hepatitis B virus and liver enzymes (ALT and AST) were tested at regular intervals as recommend by the International Committee on Thrombosis and Hemostasis. Lastly, a retrospective study evaluated 155 patients.

Study results

Clinical efficacy of Humate-P® in the control of bleeding in patients with VWD

A summary of the number of patients and bleeding episodes treated, by VWD type and corresponding efficacy rating is provided in **Table 10**. Some patients had more than one bleeding episode during the study. The efficacy rating was excellent/good in 100% of bleeding episodes treated in type 1 (13 patients, 32 episodes), 2A (2 patients, 17 episodes) and 2B (10 patients, 60 episodes) patients. In type 3 patients, 95% of the bleeding episodes (198 of 208 episodes) were rated as excellent/good and a poor (or no) response was observed in the remaining 5% of bleeding episodes (10 of 208 episodes) treated. Three of 21 type 3 patients experienced at least one bleeding episode where response was categorized as poor (or no) response.

Table 10: 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 EPISODES	32	17	60	208
Excellent/good	32 100%	17 100%	60 100%	198 95%
Poor/none	- -	- -	- -	10 5%

Note: For type 1, 13 patients experienced 32 episodes, for type 2A, 2 patients experienced 17 episodes, etc.

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 11**. 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% (74 of 82 episodes) and 96% (43 of 45 episodes) of the bleeding episodes were rated as excellent/good and a poor/none response was observed in the remaining 10% (8 of 82 episodes) and 4% (2 of 45 episodes) of the bleeding episodes, respectively.

Table 11: 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 EPISODES	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 episodes is summarized in **Table 12**. Overall, the median daily dose of Humate-P® per infusion used to treat surgical events was 69.1 IU vWF:RCof/kg (range 11.9-222.8); bleeding 55.3 IU vWF:RCof/kg (range 17.1-227.5); prophylaxis 41.6 IU vWF:RCof/kg (range 34.6-81.0); and "other" events was 51.6 IU vWF:RCof/kg (range 7.7-225.0). Similar median dosing values were obtained for the treatment of bleeding episodes in patients with VWD types 1, 2B, and 3. The median dose of Humate-P® administered to these patients was between 45-55 IU vWF:RCof/kg. In contrast, the median amount of study product administered to bleeding type 2A VWD patients in this study (17 treatment events) was slightly higher at approximately 70 IU vWF:RCof/kg. This study showed that the majority of treatments were completed within 2-3 days. Approximately 26% (83 of 318) of bleeding episodes needed treatment after the first day following the initial event.

Table 12: Summary of dosing information for bleeding episodes

TYPE/LOCATION						
		Digestive System	Nose + Mouth + Pharynx	Integument System	Female Genital System	Musculo-skeletal
No. of Episodes (Patients)[1]		49 (14)	130 (29)	22 (11)	9 (4)	108 (22)
No. of Loading Doses[2]		37	127	22	7	107
Loading Dose (IU vWF:RCof/kg)	Mean	62.1	66.9	73.4	88.5	50.2
	SD	31.1	24.3	37.7	28.3	24.9
No. of Maintenance Doses		250	55	4	15	121
Maintenance Dose (IU vWF:RCof/kg)	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 Episode	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[3]	No. of Episodes (Patients)	49 (14)	130 (29)	22 (11)	9 (4)	108 (22)
Day 2	No. of Episodes (Patients)	41 (13)	12 (9)	3 (3)	1 (1)	26 (15)
Day 3	No. of Episodes (Patients)	25 (12)	9 (6)	-	3 (2)	18 (10)

[1] Patients may have multiple bleeding episodes.
[2] Number of infusions where the dose per kg bodyweight was available. Loading dose is defined as the first dose given to a patient for a treatment episode.
[3] Day 1 = First treatment day.

Safety and hemostatic efficacy of Humate-P® in subjects with VWD undergoing surgery

In both the US and European studies, assessment of hemostatic efficacy were performed at the end of surgery, 24 hours after the last Humate-P® infusion, and at the end of the study (14 days following surgery). The investigators judged hemostatic efficacy at the end of surgery as "effective" (excellent/good) in 32 (91.4%) (95% CI: 78.5% to 97.6%) of the 35 subjects in the US study and in 25 (96%) (95% CI: 82% to 99.8%) of the 26 subjects in the European study for whom data was available.

In the US study, the hemostatic efficacy of Humate-P® was classified by investigators as excellent/good for all surgical subjects. In the European study, hemostatic efficacy as assessed by the investigator at the end of the study (Day 14) was either excellent or good in all cases.

A summary of the overall hemostatic efficacy of Humate-P® in preventing excessive bleeding in subjects participating in either the US or European study is presented in **Table 13**. Humate-P® was effective in preventing excessive bleeding during and after surgery.

Table 13: Investigator's Overall Hemostatic Efficacy Assessments for the US and European Surgical Studies

	Number of Subjects	Hemostatic Assessment	
		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%

* 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 investigator's assessment 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 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 14** shows the median expected and actual estimate blood loss during surgery in the US study.

Table 14: 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.

Viral safety

In the 67 patients 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.[35]

The 26 patients 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.[36]

In the retrospective study, all 155 patients evaluated remained negative for the presence of HIV-1 antibody 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.[37]

DETAILED PHARMACOLOGY

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® 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.[38, 39]. The activity of vWF is measured as vWF:RCof.

TOXICOLOGY

Animals

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized, Humate-P® was tolerated in the dog when given in successive doses which totalled 175 U/kg.

Mice and rats tolerated single doses of 50, 100 and 200 U/kg i.v., and did not show any signs of adverse effects. In the rabbit, a single dose of 100 U/kg i.v. had no deleterious effect.

Administration of 3 mL of a preparation containing 25 U/mL injected slowly into the blocked peripheral ear vein of rabbits caused no local effects.

Longer term studies in animals are not possible because of the development of anaphylaxis, probably as a result of the foreign protein being administered.

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PART III: CONSUMER INFORMATION

Humate-P®

Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized.

This leaflet is part III of a three-part "Product Monograph" published when Humate-P® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Humate-P®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Humate-P® is a medication used to treat adults with classical hemophilia (hemophilia-A). Humate-P® is also used to treat adults and children with Von Willebrand disease (VWD).

What it does:
Hemophilia A is a hereditary disorder of blood coagulation associated with a deficiency of the antihemophilic factor VIII activity. It can result in bleeding into joints, muscles or internal organs.

Von Willebrand disease (VWD) is caused by abnormalities of the von Willebrand Factor (vWF), a protein found in blood that supports platelet adhesion to the walls of blood vessels and allows blood vessels to stop bleeding and eventually to coagulate.

Humate-P® is a combination of two proteins found in human blood: Antihemophilic Factor and von Willebrand Factor (vWF). Both of these factors are useful for your body to have an adequate response to bleeding. The administration of Humate-P® results in an increased level of these factors in the plasma.

When it should not be used:
Do not use Humate-P® for the treatment of other coagulation factor deficiencies, such as factors II, VII, IX and X.

Humate-P® should not be used if:

- You experienced in the past a severe allergic reaction to it, immune globulins or any ingredient in the formulation.

What the medicinal ingredient is:
Humate-P®is a combination of two proteins found in human blood: Antihemophilic Factor and von Willebrand Factor (vWF).

What the important non medicinal ingredients are:
The non-active ingredients in the dried powder are albumin, glycine, sodium citrate and sodium chloride.

What dosage forms it comes in:
Humate-P® is an injectable medication that is given by intravenous infusion (injected in a vein). It is available in single dose vials as a dried, pasteurized powder. International unit activity of Factor VIII and vWF:RCof is stated on the carton and label of each vial.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Serious thromboembolic events have been reported in patients with von Willebrand disease who are treated with coagulation factor replacement therapy. Before using Humate-P®, talk to your health professional to identify any known risk factor.

Because this product is made from human plasma, a certain risk of virus transmission, such as hepatitis and HIV, or other infectious agents is present. This risk has been reduced by verifying if the donors of the plasma used to manufacture Humate-P® had prior exposure to certain viruses, by testing for the presence of certain current viral infections and by inactivating and/or removing certain viruses during the fabrication process of the drug product.

BEFORE your Humate-P® injection, talk to your health professional if:

- you are pregnant or you are breast feeding;
- your blood type is A, B or AB
- you are currently treated with any products derived from human blood or plasma, in which case you should be appropriately vaccinated

INTERACTIONS WITH THIS MEDICATION

Even if there are no known interactions between Humate-P® and other products (drug, food, herb), you should tell your health professional if you are using any other medication or natural products. You should also advise your health professional before laboratory test.

PROPER USE OF THIS MEDICATION

Usual dose:
Humate-P® is usually given as an intravenous infusion at different interval during the day. Treatment may be repeated for up to 7 days.

Every patient is different; your health professional will determine what dose of Humate-P® is right for you and how often you should receive it.

Instructions for administration:

1. Before infusion, ensure that Humate-P® and diluent vial are at room temperature.

2. Remove the Humate-P® and diluent vial flip caps to expose central portions of the rubber stoppers.

3. Wipe the surface of rubber stoppers with an antiseptic solution such as an alcohol swab and allow to dry prior to opening the Mix2Vial™ package.

4. Open the Mix2Vial™ package by peeling away the lid (Fig. 1). To maintain sterility, leave the Mix2Vial™ in the clear outer packaging. Place the diluent vial on an even surface and hold the vial tight. Grip the Mix2Vial™ together with the clear packaging and firmly snap the blue end onto the diluent stopper (Fig. 2).

Fig. 1

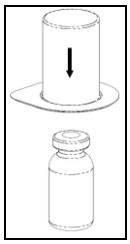

Fig. 2

5. While holding onto the diluent vial, carefully remove the clear outer packaging from the Mix2Vial™ set. Make sure that you only pull up the clear outer packaging and not the Mix2Vial™ set (Fig. 3).

Fig. 3

6. With the product vial firmly on a surface, invert the diluent vial with set attached and firmly snap the transparent adapter onto the product vial stopper (Fig. 4). The diluent will automatically transfer into the product vial.

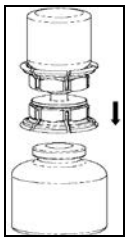

Fig. 4

7. With the diluent and product vial still attached, gently swirl the product vial to ensure the product is fully dissolved (Fig. 5). Do not shake vial.

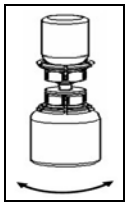

Fig. 5

8. With one hand grasp the product-side of the Mix2Vial™ set and with the other hand grasp the blue diluent-side of the Mix2Vial™ set and unscrew the set into two pieces (Fig. 6).

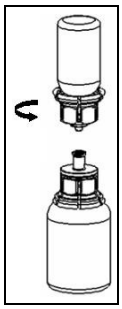

Fig. 6

9. Draw air into an empty, sterile syringe. While the product vial is upright, screw the syringe to the Mix2Vial™ set. Inject air into the product 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).

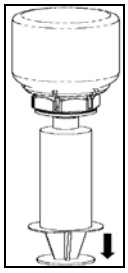

Fig. 7

10. 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™ (Fig. 8). Attach the syringe to a venipuncture set.

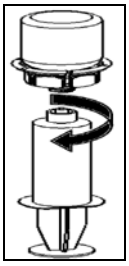

Fig. 8

11. If the same patient is to receive concentrate from more than one vial, the contents of two vials may be drawn into the same syringe through a separate unused Mix2Vial™ set before attaching the vein needle.

12. 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 after reconstitution. To assure product sterility, Humate –P® should be administered within three hours after reconstitution.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Humate-P® is usually tolerated without reaction. Some unwanted side effects are chills, hot flushes, abnormal sensations such as numbness or burning.

Talk to your health professional immediately if you think you have any of those reactions:

- skin rash, tightness in the chest or itching
- pain in the legs or extremities
- swelling
- unusual bleedings
- abdominal pain

This is not a complete list of side effects. For any unexpected effects while taking Humate-P®, contact your health professional.

HOW TO STORE IT

Store at room temperature, up to 25°C, for the period indicated by the expiration date on its label. Avoid freezing, which may damage the diluent container.

Do not use the product after the expiration date. Keep the vial in its box during storage.

Humate-P® is supplied in single-use vials. It contains no preservatives, so any unused portion should be discarded immediately after injection.

Keep Humate-P® out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect*
- Call toll-free to 1-866-234-2345;
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca medeffect.

NOTE: Should you require information related to the Management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

We recommend that CSL Behring Canada be copied when reporting suspected side effects, at the following address:
adversereporting@cslbehring.com

or be informed by pager
Pager Number: 1-613-783-1892

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at:
http://www.cslbehring.ca
or by contacting the sponsor, CSL Behring Canada, Inc.
at: 1-613-783-1892.

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