



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Antihemophilic Factor/Von Willebrand Factor Complex (Humate-P®)

Von Willebrand Factor/Coagulation Factor VIII Complex (Wilate®)

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Coverage Policy Number 8007

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Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers antihemophilic factor/von Willebrand factor complex (Humate-P®) as medically necessary for EITHER:

- treatment and prevention of bleeding in hemophilia A in adults
- von Willebrand disease (VWD) for **EITHER** of the following indications when there is failure, contraindication or intolerance to desmopressin:
 - treatment of spontaneous and/or trauma-induced bleeding episodes
 - prevention of excessive bleeding during and/or following surgery

CIGNA covers von Willebrand factor/coagulation factor VIII complex (Wilate®) as medically necessary for the treatment of spontaneous and/or trauma-induced bleeding episodes in individuals with severe von Willebrand disease (VWD) or individuals with mild or moderate VWD when there is failure, contraindication or intolerance to desmopressin.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to antihemophilic factor/von Willebrand factor complex (Humate-P®) or von Willebrand factor/coagulation factor VIII complex (Wilate®) therapy.

FDA Approved Indications

Humate-P

Humate-P is an Antihemophilic Factor/von Willebrand Factor (VWF) Complex (Human) indicated for Hemophilia A – treatment and prevention of bleeding in adults and Von Willebrand disease (VWD) – in adults and pediatric patients in the treatment of spontaneous and trauma-induced bleeding episodes; it is not indicated for the prophylaxis of spontaneous bleeding episodes, and for the prevention of excessive bleeding during and after surgery. This applies to patients with severe VWD as well as patients with mild to moderate VWD where the use of desmopressin is known or suspected to be inadequate. Humate-P is not indicated for the prophylaxis of spontaneous bleeding episodes.

Wilate

Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. Wilate is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients. Wilate is also not indicated for Hemophilia A

FDA Recommended Dosing

Humate-P

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 general dosages in following table are recommended for adult patients:

Dosage Recommendations for the Treatment of Hemophilia A	
Hemorrhagic Event	Dosage (IU FVIII:C/kg body weight)
Minor hemorrhage: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Major operations • Gastrointestinal bleeding • Neck, tongue or pharyngeal hematoma with 	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

<ul style="list-style-type: none"> potential for airway compromise Intracranial, intraabdominal or intrathoracic bleeding Fractures 	FVIII:C level at 30-50% of normal
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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. 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 2.0 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 5 IU/dL. The following table provides dosing guidelines for pediatric and adult patients:

VWF:RCo Dosing Recommendations for the Treatment of von Willebrand Disease		
Classification of VWD	Hemorrhage	Dosage (IU VWF:RCo/kg body weight)
Type 1 <ul style="list-style-type: none"> mild, if desmopressin is inappropriate (Baseline VWF:RCo activity typically >30%) moderate or severe (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 trough 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)
	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 trough 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.
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 trough 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.

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. VWF:RCo and FVIII:C be assessed in all patients prior to surgery. Measure IVR as follows:

1. Measure baseline plasma VWF:RCo.
2. Infuse 60 IU VWF:RCo/kg product intravenously at time 0
3. At time +30 minutes, measure plasma VWF:RCo

Calculation of the loading dose requires four values: the target peak plasma VWF:RCo level, the baseline VWF:RCo level, body weight (BW) in kilograms, and IVR. When individual recovery values are not available, a

standardized loading dose can be used based on an assumed VWF:RCo IVR of 2.0 IU/dL per IU/kg of WF:RCo product administered.

Wilate

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders. Each vial of Wilate contains the labeled amount in International Units (IU) of von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo), and coagulation factor VIII (FVIII) activity measured with the chromogenic substrate assay. The number of units of VWF:RCo and FVIII activities administered is expressed in IU, which are related to the current WHO standards for VWF and FVIII products. VWF:RCo and FVIII activities in plasma are expressed either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for VWF:RCo and FVIII activities in plasma). The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1. The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required. The careful control of replacement therapy is especially important in life-threatening hemorrhages. When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity. The following table contains recommended dosing for Wilate:

Wilate Dosing Recommendations for vWD			
Type of Hemorrhages	Loading Dosage (IU VWF:RCo /kg BW)	Maintenance Dosage (IU VWF:RCo /kg BW)	Therapeutic Goal
Minor	20-40 IU/kg	20-30 IU/kg every 12-24 hours	VWF:RCo and FVIII activity trough levels of >30%
Major	40-60 IU/kg	20-40 IU/kg every 12-24 hours	VWF:RCo and FVIII activity trough levels of >50%

Drug Availability

Humate-P

Humate-P is supplied in a single-dose vial containing the labeled amount of VWF:RCo and FVIII activity expressed in International Units (IU). Each package contains a vial of Humate-P, a vial of diluent containing sterile water, a Mix2Vial filter transfer set, and two alcohol swabs.

Wilate

Wilate is supplied in a package with a single-dose vial of powder and a vial of diluent together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set and two alcohol swabs. • Each vial of Wilate contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay.

General Background

Pharmacology

Humate-P

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). Humate-P consists of two different non-covalently bound proteins (Factor VIII and VWF). Factor VIII is an essential co-factor 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 pro-coagulant protein Factor VIII.

After intravenous injection of Humate-P, in humans, there is a rapid increase of plasma Factor VIII activity 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).

Wilate

Wilate is a human plasma-derived, sterile, purified, double virus inactivated von Willebrand Factor/Coagulation Factor VIII Complex (Human). Wilate is labeled with the actual VWF:RCo and FVIII activities in IU per vial. The VWF activity (VWF:RCo) is determined using a manual agglutination method referenced to the current "WHO International Standard for von Willebrand Factor Concentrate". The FVIII activity is determined using a chromogenic substrate assay referenced to the current "WHO International Standard for Human Coagulation Factor VIII Concentrate". The assay methodologies are according to European Pharmacopoeia (Ph.Eur.).

Adverse Reactions/Contraindications

Humate-P

Humate-P is contraindicated in individuals with a history of anaphylactic or severe systemic response to anti-hemophilic factor or VWF preparations. It is also contraindicated in individuals with a known hypersensitivity to any of its components.

The safety and effectiveness of Humate-P for the treatment of VWD was demonstrated in 26 pediatric subjects, including infants, children, and adolescents but has not been evaluated in neonates. The safety of Humate-P for the prevention of excessive bleeding during and after surgery was demonstrated in 8 pediatric subjects (ages 3 through 15) with VWD, of the 34 pediatric subjects studied for both treatment of VWD and prevention of excessive bleeding during and after surgery, four were infants (1 month to under 2 years of age), 23 were children (2 through 12 years), and 7 were adolescents (13 through 15 years).

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. The most commonly reported side effects of Humate-P are allergic-anaphylactic reactions including urticaria, chest tightness, rash, pruritus, edema, and shock. For patients undergoing surgery, the most common adverse reactions are post-operative wound or injection site bleeding.

Wilate

Wilate is contraindicated for patients who have known anaphylactic or severe systemic reaction to plasma-derived products, any ingredient in the formulation, or components of the container.

The most common adverse reactions to treatment with Wilate in patients with VWD have been urticaria and dizziness. The most serious adverse reactions to treatment with Wilate in patients with VWD have been hypersensitivity reactions.

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

There were 92 VWD patients who received Wilate on 5676 occasions including clinical studies that involved prophylactic use, treatment on demand, surgery, and pharmacokinetics. Their safety data showed that the most common adverse reactions were urticaria and dizziness (each with 2 patients; 2.2%). There were also four patients (4.4%) who showed seroconversion for antibodies to parvovirus B19 not accompanied by clinical signs of disease. Seroconversion has not been reported since implementation of minipool testing of plasma used for the manufacture of Wilate.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J7184	Injection, von Willebrand factor complex (human), Wilate, per 100 IU VWF RCO (code deleted 06-30-2011)
J7186	Injection, antihemophilic factor VIII/von Willebrand factor complex (human), per factor VIII IU
J7187	Injection, von Willebrand factor complex (Humate-p), per IU VWF:RCO
Q2041	Injection, von Willebrand factor complex (human), Wilate, per 1 IU VWF RCO (Code effective 07-01-2011)

ICD-9-CM Diagnosis Codes	Description
286.0	Congenital factor VIII disorder
286.4	von Willebrand's disease

References

1. CSL Behring LLC. Antihemophilic Factor/von Willebrand Factor Complex (Human), Dried, Pasteurized (Humate-P[®]) package insert. Kankakee, IL: CSL Behring LLC. Jan 2010.
2. Federici AB, Castaman G, Franchini M, Morfini M, Zanon E, Coppola A, Tagliaferri A, Boeri E, Mazzucconi MG, Rossetti G, Mannucci PM. Clinical use of Haemate P in inherited von Willebrand's disease: a cohort study on 100 Italian patients. Haematologica. 2007 Jul;92(7):944-51.
3. McEvoy GK, ed. AHFS 2010 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2010.
4. Octopharma USA, Inc. von Willebrand Factor/Coagulation Factor VIII Complex (Human) (Wilate[®]) prescribing information. Hoboken, NJ: Octopharma USA, Inc. Dec 2009.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	6/15/2008	8007	Antihemophilic Factor/Von Willebrand Factor Complex (Human), Dried, Pasteurized (Humate-P [®])
Great-West Healthcare	1/2007	P05.102.1	Hemophilia

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