



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 Hemophilia Factor Replacement

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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

Factor VIIa

CIGNA covers recombinant coagulation Factor VIIa as medically necessary for ANY of the following indications:

- treatment of bleeding episodes hemophilia A or B **with inhibitors (i.e., antibodies) to Factor VIII or Factor IX** and acquired hemophilia
- treatment of bleeding episodes in congenital Factor VII deficiency
- prevention of bleeding in surgical or invasive procedures in hemophilia A or B **with inhibitors (i.e., antibodies) to Factor VIII or Factor IX** and in acquired hemophilia
- prevention of bleeding in surgical or invasive procedures in congenital Factor VII deficiency

Factor VIII

CIGNA covers factor VIII therapy as medically necessary for ANY of the following indications:

- hemophilia A
- acquired hemophilia
- disseminated intravascular coagulation (treatment adjunct)
- Kasabach-Merritt syndrome (treatment adjunct)
- von Willebrand disease
- hypofibrinogenemia

Factor IX

CIGNA covers Factor IX Therapy as medically necessary for the prevention or treatment of bleeding in individuals with Factor IX deficiency due to Hemophilia B.

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 Recombinant Coagulation Factor VIIa, Factor VIII therapy, and Factor IX therapy.

FDA Approved Indications Factor VIIa

Factor VIIa Products

Brand Name	Approved Indication
Novoseven RT	<ul style="list-style-type: none">• Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia• Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX and in patients with acquired hemophilia• Treatment of bleeding episodes in patients with congenital FVII deficiency• Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency

Factor VIII

Factor VIII Products

Brand Name	Approved Indication
Advate Bioclata Genarc Helixate FS Kogenate FS Recombinate ReFacto Xyntha	Antihemophilic factor (recombinant) indicated in hemophilia A (classical hemophilia or congenital factor VIII deficiency) for the control and prevention of bleeding episodes and for perioperative management of adults and children with hemophilia A.
Alphanate	Antihemophilic factor/von Willebrand factor complex (human) - indicated for the prevention and control of bleeding in patients with Factor VIII deficiency due to Hemophilia A or acquired Factor VIII Deficiency. It is also indicated for surgical and/or invasive procedures in patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated.
Hemofil M Monarc-M	Antihemophilic factor (human) indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes.
Koate-DVI	Antihemophilic factor (human) indicated for the treatment of hemophilia A (classical hemophilia) in which there is a demonstrated deficiency of activity of the plasma clotting factor, factor VIII. It is also provides a means of temporarily replacing the missing clotting factor in order to correct or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia.
Monoclata-P	Antihemophilic factor (human) indicated for treatment of hemophilia A (classical hemophilia). Affected individuals frequently require therapy following minor accidents. Surgery, when required in such individuals, must be preceded by temporary corrections of the clotting abnormality. Surgical prophylaxis in severe AHF deficiency can be accomplished with an appropriately-dosed pre-surgical IV bolus of Monoclata-P [®] followed by intermittent maintenance doses.

Factor IX

Factor IX Products

Human Factor IX Therapy	
Brand Name	Approved Indication
Alphanine SD	AlphaNine SD is indicated for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. AlphaNine SD contains low, non-therapeutic levels of Factors II, VII, and X, and, therefore, is not indicated for the treatment of Factor II, VII or X deficiencies. This product is also not indicated for the reversal of coumadin anticoagulant-induced hemorrhage, nor in the treatment of hemophilia A patients with inhibitors to Factor VIII.
Mononine	Mononine is indicated for the prevention and control of bleeding in Factor IX deficiency, also known as Hemophilia B or Christmas disease. Mononine is not indicated in the treatment or prophylaxis of Hemophilia A patients with inhibitors to Factor VIII. Mononine contains non-detectable levels of Factors II, VII and X and is, therefore, not indicated for replacement therapy of these clotting factors. Mononine is also not indicated in the treatment or reversal of coumadin-induced anticoagulation or in a hemorrhagic state caused by hepatitis-induced lack of production of liver dependent coagulation factors.
Complex Factor IX Therapy	
Brand Name	Approved Indication
Bebulin VH	Bebulin VH, Factor IX Complex, Vapor Heated is indicated for the prevention and control of hemorrhagic episodes in hemophilia B patients. Bebulin VH, Factor IX Complex, Vapor Heated is not indicated for use in the treatment of Factor VII deficiency. No clinical studies have been conducted to show benefit from this product for treating deficiencies other than Factor IX deficiency.
Proplex T	Proplex T, Factor IX Complex, Heat Treated is indicated for: 1. Factor IX deficiency (Hemophilia B, Christmas disease). The intravenous administration of PROPLEX T, Factor IX Complex, Heat Treated is intended to prevent or control bleeding episodes in patients with this deficiency. Factor IX Complex should not be used in patients with mild Factor IX deficiency for whom fresh frozen plasma is effective 2. Bleeding episodes in patients with inhibitors to Factor VIII 3. Factor VII deficiency. The Factor VII content present in Proplex T, Factor IX Complex, Heat Treated has been shown to be effective in prevention or control of bleeding episodes in patients with Factor VII deficiency.
Profilnine SD	Factor IX Complex, Profilnine SD is indicated for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. This product contains non-therapeutic levels of Factor VII, and is not indicated for use in the treatment of Factor VII deficiency.
Recombinant Factor IX Therapy	
Brand Name	Approved Indication
Benefix	Control and prevention of bleeding episodes in hemophilia B: Benefix, Coagulation Factor IX (Recombinant), is indicated for the control and prevention of bleeding episodes in adult and pediatric patients with hemophilia B (congenital factor IX deficiency or Christmas disease). Peri-operative management in patients with hemophilia B: BeneFIX Benefix, Coagulation Factor IX (Recombinant), is indicated for peri-operative management in adult and pediatric patients with hemophilia B. Benefix, Coagulation Factor IX (Recombinant), is NOT indicated for: treatment of other factor deficiencies (e.g., factors II, VII, VIII, and X), treatment of hemophilia A patients with inhibitors to factor VIII, reversal of coumadin-induced anticoagulation, or treatment of bleeding due to low levels of liver-dependent coagulation factors.

FDA Recommended Dosing Factor VIIa

Novoseven RT

Indication	Recommended Dosing
Hemophilia A or B with Inhibitors for Treatment of Acute Bleeding Episodes - Hemostatic Dosing	Administer 90 micrograms/kg given every two hours by bolus infusion until hemostasis is achieved, or until the treatment has been judged to be inadequate. The minimum effective dose has not been established. For patients treated for joint or muscle bleeds, a decision on outcome was

	reached for a majority of patients within eight doses although more doses were required for severe bleeds.
Post-Hemostatic Dosing	The appropriate duration of post-hemostatic dosing has not been studied. For severe bleeds, dosing should continue at 3-6 hour intervals after hemostasis is achieved, to maintain the hemostatic plug. Patients should be appropriately monitored by a physician experienced in the treatment of hemophilia during this time period.
Minor Surgery	An initial dose of 90 micrograms per kg body weight should be given immediately before the intervention and repeated at 2-hour intervals for the duration of the surgery. For minor surgery, post-surgical dosing by bolus injection should occur at 2-hour intervals for the first 48 hours and then at 2- to 6-hour intervals until healing has occurred.
Major Surgery	An initial dose of 90 micrograms per kg body weight should be given immediately before the intervention and repeated at 2-hour intervals for the duration of the surgery. For major surgery, post-surgical dosing by bolus injection should occur at 2 hour intervals for 5 days, followed by 4 hour intervals until healing has occurred. Additional bolus doses should be administered if required.
Congenital Factor VII deficiency	The recommended dose range for treatment of bleeding episodes or for prevention of bleeding in surgical interventions or invasive procedures in congenital Factor VII deficient patients is 15-30 micrograms per kg body weight every 4-6 hours until hemostasis is achieved. Effective treatment has been achieved with doses as low as 10 micrograms/kg. Dose and frequency of injections should be adjusted to each individual. The minimum effective dose has not been determined.
Acquired Hemophilia	The recommended dose range for the treatment of patients with acquired hemophilia is 70-90 micrograms/kg repeated every 2-3 hours until hemostasis is achieved. The minimum effective dose in acquired hemophilia has not been determined.

Factor VIII

Factor VIII Products

Brand Name	Recommended Dosing
Advate Bioclata Genarc Helixate FS Kogenate FS Recombinate ReFacto Xyntha Alphanate Hemofil M Monarc-M Koate-DVI Monoclata-P	<p>The dose of factor VIII must be individualized for each patient based on patient weight, circulating antibody concentration, type of hemorrhage and desired plasma factor VIII concentration. The following formulas may be used as guides in determining dosage:</p> $\text{Desired AHF increase (\% of normal)} = \left(\frac{[\text{Dose AHF (IU)}]}{[\text{Body weight (kg)}]} \right) \times 2$ $\text{Dose AHF (IU)} = \text{Body weight (kg)} \times \text{Desired AHF increase} \times 0.5$

Factor IX

Factor IX Products

Human Factor IX Therapy	
Brand Name	Recommended Dosing
Alphanine SD Mononine	Varies with each individual and depends upon the circumstances. Each vial of factor IX concentrate is labeled with the factor IX activity expressed in International Units (IU) per vial. This potency assignment is referenced to the World Health Organization International Standard. One IU of factor IX activity per kg of body weight is approximately equal to the factor IX activity in 1 mL of fresh plasma and increases the plasma concentration of factor IX by 1%. The following formula may be used as a guide in determining the number of units to be

	administered: Body Weight (in kg) x Desired increase in Plasma Factor IX (Percent) x 1.0 IU/kg = Number of Factor IX IU Required
Complex Factor IX Therapy	
Brand Name	Recommended Dosing
Bebulin VH Proplex T Profilnine SD	Varies with each individual and depends upon the circumstances. Each vial of factor IX concentrate is labeled with the factor IX activity expressed in International Units (IU) per vial. This potency assignment is referenced to the World Health Organization International Standard. One IU of factor IX activity per kg of body weight is approximately equal to the factor IX activity in 1 mL of fresh plasma and increases the plasma concentration of factor IX by 1%. The following formula may be used as a guide in determining the number of units to be administered: Body Weight (in kg) x Desired increase in Plasma Factor IX (Percent) x 1.0 IU/kg = Number of Factor IX IU Required
Recombinant Factor IX Therapy	
Brand Name	Recommended Dosing
Benefix	Varies with each individual and depends upon the circumstances. Each vial of factor IX concentrate is labeled with the factor IX activity expressed in International Units (IU) per vial. This potency assignment is referenced to the World Health Organization International Standard. One IU of factor IX activity per kg of body weight is approximately equal to the factor IX activity in 1 mL of fresh plasma and increases the plasma concentration of factor IX by 1%. The following formula may be used as a guide in determining the number of units to be administered: Body Weight (in kg) x Desired increase in Plasma Factor IX (Percent) x 1.0 IU/kg = Number of Factor IX IU Required

As a general rule, the level of Factor IX required for treatment of different conditions is as follows:

	Minor Spontaneous Hemorrhage, Prophylaxis	Major Trauma or Surgery
Desired levels of Factor IX for hemostasis	15-25% [or IU/dL]	25-50% [or IU/dL]
Initial loading dose to achieve desired level	20-30 IU/kg	up to 75 IU/kg
Frequency of dosing	Once; repeated in 24 hours if necessary	every 18-30 hours, depending on T $\frac{1}{2}$ and measured Factor IX levels
Duration of treatment	Once; repeated if necessary	Up to ten days, depending upon nature of insult

There are no data directly comparing the efficacy or safety of the Factor IX products. There are no data or guidelines assessing whether these products are equivalent or interchangeable. Each product is slightly different based on the production method. Products completely free from human or animal protein have the least potential for disease transmission. Current guidelines and recommendations from hemophilia organizations do not advocate one Factor IX over another for treatment or prophylaxis.

Black Box Warning

Factor VIIa

Serious thrombotic adverse events are associated with the use of NovoSeven RT outside labeled indications. Arterial and venous thrombotic and thromboembolic events following administration of NovoSeven have been reported during post-marketing surveillance. Clinical studies have shown an increased risk of arterial thromboembolic adverse events with NovoSeven RT when administered outside the current approved indications. Fatal and non-fatal thrombotic events have been reported. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to

patients who will receive NovoSeven RT. Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis.

Drug Availability

Factor VIIa

NovoSeven RT Coagulation Factor VIIa (Recombinant) Room Temperature Stable is supplied as a white, lyophilized powder in single-use vials, one vial per carton. The vials are made of glass, closed with a latex-free, chlorobutyl rubber stopper, and sealed with an aluminum cap. The vials are equipped with a snap-off polypropylene cap. The amount of rFVIIa in milligrams and in micrograms is stated on the label as follows: 1 mg per vial (1000 micrograms/vial), 2 mg per vial (2000 micrograms/vial), and 5 mg per vial (5000 micrograms/vial).

Factor VIII

For drug availability of each agent please refer to corresponding prescribing information from the drug manufacturer.

Factor IX

For drug availability of each agent please refer to corresponding prescribing information from the drug manufacturer.

General Background

Factor VIIa

Pharmacology

Recombinant coagulation Factor VIIa (NovoSeven RT) is a vitamin K-dependent glycoprotein that is structurally similar to human plasma-derived Factor VIIa. It promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. When complexed with tissue factor, it can activate coagulation Factor X to Factor Xa, and Factor IX to Factor IXa. Activated Factor X (Factor Xa), complexed with other factors converts prothrombin to thrombin and fibrinogen to fibrin to form a hemostatic plug, inducing local hemostasis. Recombinant coagulation Factor VIIa (rFVIIa) is used for the prevention and control of hemorrhagic episodes in certain patients with hemophilia A (i.e., antihemophilic factor [Factor VIII] deficiency; classic hemophilia) or hemophilia B (i.e., Factor IX deficiency; Christmas disease) who have developed inhibitors (alloantibodies) to Factor VIII or Factor IX.

RFVIIa is one of several therapeutic options that can be used for the prevention and control of bleeding in hemophilia patients with inhibitors. The treatment of choice depends on several factors including the severity and location of the bleed, level and type of inhibitors, and whether the patient has a history of an anamnestic increase in inhibitor levels following use of preparations containing Factor VIII or Factor IX. There are no controlled studies to date that directly compare the safety and efficacy of rFVIIa with other available options including - antihemophilic factor (porcine), anti-inhibitor coagulant complex (i.e., activated prothrombin complex concentrate [APCC]), and Factor IX complex (i.e., prothrombin complex concentrate [PCC]).

Adverse Reactions/ Contraindications

Thrombotic events are the most serious adverse reactions observed in patients receiving rFVIIa; however, the extent of the risk of thrombotic adverse events after treatment in individuals with hemophilia and inhibitors is considered to be low. The most common adverse reactions observed in clinical studies for all labeled indications of rFVIIa include: fever, hemorrhage, injection site reaction, arthralgia, headache, hypertension, hypotension, nausea, vomiting, pain, edema, and rash.

Recombinant coagulation Factor VIIa is contraindicated in patients with known hypersensitivity to any of the following: rFVIIa or any of its components; mouse, hamster, or bovine proteins. The extent of the risk of thrombotic adverse events after treatment with rFVIIa in patients with hemophilia and inhibitors is not known, but is considered to be low. Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with APCCs/PCCs may have an increased risk of developing thrombotic events due to circulating tissue factor (TF) or predisposing coagulopathy. In patients without hemophilia, the extent of the risk of arterial and venous thromboembolic adverse events after treatment with rFVIIa is also not known. A clinical study in elderly non-hemophilia intracerebral hemorrhage patients indicated a potential increased risk of arterial thromboembolic adverse events with use of rFVIIa, including myocardial ischemia, myocardial infarction, cerebral ischemia and/or infarction. Due to limited clinical studies

which clearly address the effect of post-hemostatic dosing, precautions should be exercised when rFVIIa is used for prolonged dosing.

Factor VIII

Pharmacology

Factor VIII, or antihemophilic factor, is an endogenous glycoprotein necessary for blood clotting and hemostasis. It is a cofactor necessary for factor IX to activate factor X in the intrinsic pathway. In hemophilia A (classical hemophilia), there is a deficiency of this clotting factor. The average normal plasma activity of factor VIII is designated as 100%, and a factor VIII concentration of 25% of normal is required for hemostasis. Patients with severe hemophilia have a factor VIII concentration of less than 1% of normal and frequently experience bleeding even in the absence of trauma. Patients with a factor VIII concentration between one and 5% (moderate hemophilia) experience less bleeding, and patients with a factor VIII concentration greater than 5% (mild hemophilia) usually experience bleeding only after obvious trauma. The administration of factor VIII temporarily replaces the missing clotting factor to correct or prevent bleeding episodes.

Factor VIII is obtained from pooled human plasma, or produced by recombinant deoxyribonucleic acid (DNA) technology. Almost all of the plasma-derived factor VIII products currently available are sterile, nonpyrogenic, high-purity concentrates purified by gel permeation chromatography, ion exchange chromatography or immunoaffinity chromatography utilizing murine monoclonal antibodies to factor VIII or von Willebrand factor (vWf). However, to date, no procedure has been shown to be totally effective in removing the risk of viral infection from coagulant factor concentrates. The purified concentrates contain 50–150 times as much factor VIII as an equal volume of fresh plasma. Some products contain albumin as a stabilizer, and monoclonal purified products contain trace amounts of mouse protein. Human recombinant factor VIII is a sterile, nonpyrogenic concentrate with biologic activity comparable to that of plasma-derived factor VIII. Human recombinant factor VIII contains albumin as a stabilizer and trace amounts of mouse, hamster, and bovine proteins. Cryoprecipitated factor VIII is a sterile, frozen concentrate of human factor VIII obtained from the plasma of one unit of whole blood or from one or more units of single-donor fresh-frozen plasma.

There are no data specifically addressing the equivalence or interchangeability of the factor VIII products. Recombinant factor VIII is recommended as the treatment of choice for patients with hemophilia A by the United Kingdom Haemophilia Center Doctors' Organization (UKHCDO) and National Hemophilia Foundation (including patients with inhibitor titers < 10 Bethesda units (BU) per ml to control and prevent bleeding episodes and for surgical prophylaxis). Because there is insufficient product available in Italy to treat all patients with hemophilia A with recombinant factor VIII products, the Italian guidelines prioritize the use of recombinant factor VIII for previously untreated patients. None of these guidelines advocate one recombinant factor VIII product over another; however, the UKHCDO guidelines do recommend using products completely free of human or animal protein when possible, as these are the safest products available.

Factor IX

Pharmacology

Factor IX (human) is a highly purified concentrate of factor IX and contains only non-therapeutic concentrations of factors II, VII and X. Therefore, factor IX (human) should not be used for replacement treatment of factor II, VII, or X deficiencies or for the treatment or reversal of coumadin anticoagulant-induced hemorrhage or hemorrhagic states caused by hepatitis-induced lack of production of liver-dependent coagulation factors. Factor IX complex (human) should not be used in the treatment of coagulation disorders involving factors II or X unless the use of fresh frozen plasma is not feasible or has been ineffective.

Factor IX half-life is 3–6 hours, with an elimination of 17–32 hours. Time to peak effect is 10–30 minutes after intravenous administration.

Adverse Reactions

Adverse effects include transient fever, chills, headache, urticaria, nausea, vomiting, somnolence, lethargy, flushing, tingling, and changes in pulse rate and blood pressure. Many of the adverse effects may be related to rapid administration of the drug and should be reduced. There is a risk of hepatitis, HIV infection, Creutzfeldt-Jakob disease or Variant Creutzfeldt-Jakob disease and West Nile virus. Use of high doses of factor IX has been associated with myocardial infarction, disseminated intravascular coagulation (DIC), venous thrombosis and pulmonary embolism.

Coding/Billing Information

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

Covered when medically necessary:

HCPCS Codes	Description
J7189	Factor VIIA (antihemophilic factor, recombinant), per 1 mcg
J7185	Injection, factor VIII (antihemophilic factor, recombinant) (XYNTHA), per IU
J7190	Factor VIII (antihemophilic factor, human) per IU
J7192	Factor VIII (antihemophilic factor, recombinant) per IU, not otherwise specified
J7193	Factor IX (antihemophilic factor, purified, nonrecombinant), per IU
J7194	Factor IX complex, per IU
J7195	Factor IX (antihemophilic factor, recombinant), per IU

ICD-9-CM Diagnosis Codes	Description
286.0	Congenital factor VIII disorder (hemophilia A)
286.1	Congenital factor IX disorder (hemophilia B)
286.3	Congenital deficiency of other clotting factors (factor VII deficiency)
286.4	Von Willebrand's disease
286.6	Defibrination syndrome
286.7	Acquired coagulation deficiency

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	8/15/2008 1/2007	4046 P05.102.1	Recombinant Factor VII Hemophilia
CIGNA HealthCare Great-West Healthcare	4/15/2008 1/2007	4025 P05.102.1	Factor VIII Therapy Hemophilia
CIGNA HealthCare Great-West Healthcare	8/15/2008 1/2007	4045 P05.102.1	Factor IX Therapy Hemophilia

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