CLOTTING FACTORS and COAGULANT BLOOD PRODUCTS

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Related Medical or Drug Policies:
None

Related Coverage Determination Guidelines:
Custodial and Skilled Care Services

INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee’s specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

This policy refers to the following products:

<table>
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<tr>
<td>Factor VIIa (recombinant)</td>
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<td>Factor XIII (plasma-derived)</td>
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NovoSeven™ (coagulation factor VIIa (recombinant))
NovoSeven® RT (coagulation factor VIIa (recombinant))
Conifact™ (factor XIII concentrate (human))
Hemofil M® (antihemophilic factor (human))
The following information provides the indications and criteria for which specific clotting factors and coagulant blood products are considered proven.*

### A. Congenital Factor XIII Deficiency (i.e., Fibrin Stabilizing Factor Deficiency)

1. Factor XIII (plasma-derived) [Corifact] is proven when used according to US Food and Drug Administration (FDA) labeled indications. Both of the following criteria must be met:
   a. Diagnosis of congenital factor XIII deficiency -AND-
   b. One of the following:
      (1) Routine prophylactic treatment -OR-
      (2) Peri-operative management of surgical bleeding

2. Coagulation Factor XIII A-subunit (recombinant) [Tretten] is proven when used according to US Food and Drug Administration (FDA) labeled indications. Both of the following criteria must be met:
   c. Diagnosis of congenital factor XIII A-subunit deficiency -AND-
   d. Used for routine prophylactic treatment for bleeding
B. **Von Willebrand Disease (VWD)**

1. Factor VIII (plasma-derived) / von Willebrand Factor Complex (plasma-derived) [Alphanate or Humate-P] is **proven** when used according to FDA labeled indications. **Both** of the following criteria must be met:²,³
   a. One of the following:
      (1) Diagnosis of severe von Willebrand disease
         - OR -
      (2) **Both** of the following:
         (a) Diagnosis of mild or moderate von Willebrand disease
         - AND -
         (b) Patient has previously tried and failed treatment with desmopressin or treatment with desmopressin is contraindicated. Refer to Benefit Considerations for specific state guidance.
   - AND -
   b. One of the following:
      (1) Treatment of spontaneous and trauma-induced bleeding episodes
         - OR -
      (2) Prevention of excessive bleeding during surgery (i.e., surgical prophylaxis)

2. Factor VIII (plasma-derived) / von Willebrand Factor Complex (plasma-derived) [Wilate] is **proven** when used according to FDA labeled indications. **One** of the following criteria must be met:⁴
   a. Both of the following:
      (1) Diagnosis of severe von Willebrand disease
         - AND -
      (2) Treatment of spontaneous and trauma-induced bleeding episodes
         - OR -
   b. Both of the following:
      (1) Diagnosis of mild or moderate von Willebrand disease
         - AND -
      (2) Patient has previously tried and failed treatment with desmopressin or treatment with desmopressin is contraindicated. Refer to Benefit Considerations for specific state guidance.

C. **Congenital Factor VII Deficiency**

1. Factor VIIa (recombinant) [NovoSeven, NovoSeven RT] is **proven** when used according to FDA labeled indications. **Both** of the following criteria must be met:⁵,⁴⁷
   a. Diagnosis of congenital factor VII deficiency
      - AND -
   b. One of the following:
      (1) Treatment of bleeding episodes
      - OR -
      (2) Prevention of bleeding in surgical interventions or invasive procedures (i.e., surgical prophylaxis)

D. **Hemophilia A (i.e., Factor VIII Deficiency, Classical Hemophilia)**

1. Factor VIII (plasma-derived) / von Willebrand Factor Complex (plasma-derived) [Alphanate or Humate-P], Factor VIII (plasma-derived) [Hemofil M, Koāte-DVI or Koāte-BDV] is **proven** when used according to FDA labeled indications. **Both** of the following criteria must be met:⁴,⁷
   a. Diagnosis of severe hemophilia
      - AND -
   b. One of the following:
      (1) Treatment of spontaneous and trauma-induced bleeding episodes
      - OR -
      (2) Prevention of excessive bleeding during surgery (i.e., surgical prophylaxis)
Monoclate-P), Factor VIII (recombinant) [Advate, Helixate FS, Kogenate FS, Novoeight, Recombinate, or Xyntha, Xyntha Solofuse] are proven when used according to FDA labeled indications. Both of the following criteria must be met:\textsuperscript{2,3,6-13,49,50}

a. Diagnosis of hemophilia A
   \textbf{-AND-}

b. One of the following:
   \begin{enumerate}
   \item Treatment of bleeding episodes
   \textbf{-OR-}
   \item Prevention of bleeding episodes
   \textbf{-OR-}
   \item Prevention of bleeding in surgical interventions or invasive procedures (e.g., surgical prophylaxis)
   \end{enumerate}

2. Anti-Inhibitor Coagulant Complex (plasma-derived) [FEIBA NF, FEIBA VH] and Factor VIIa (recombinant) [NovoSeven, NovoSeven RT] are proven when used according to FDA labeled indications. All of the following criteria must be met:\textsuperscript{5,14,20-21,48}

a. Diagnosis of hemophilia A
   \textbf{-AND-}

b. Documentation of inhibitors (e.g., Bethesda inhibitor assay)
   \textbf{-AND-}

c. One of the following:
   \begin{enumerate}
   \item Treatment of a spontaneous bleeding episode
   \textbf{-OR-}
   \item Prevention of bleeding in surgical interventions (i.e., surgical prophylaxis)
   \textbf{-OR-}
   \item Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
   \end{enumerate}

3. Factor VIII (plasma-derived) / von Willebrand Factor Complex (plasma-derived) [Alphanate] and Factor VIIa (recombinant) [NovoSeven, NovoSeven RT] are proven when used according to FDA labeled indications. Both of the following criteria must be met:\textsuperscript{2,5,32-33,47}

a. Diagnosis of acquired factor VIII hemophilia (e.g., acquired hemophilia A, Factor VIII deficiency)
   \textbf{-AND-}

b. Treatment or prevention of bleeding episodes

\section*{E. Hemophilia B (i.e., Congenital Factor IX Deficiency, Christmas Disease)}

1. Factor IX (plasma-derived) [AlphaNine SD, Bebulin, Mononine, or Profilnine SD] is proven when used according to FDA labeled indications. Both of the following criteria must be met:\textsuperscript{15-18}

a. Diagnosis of hemophilia B
   \textbf{-AND-}

b. Prevention and treatment of bleeding episodes

2. Factor IX (recombinant) [BeneFIX or Rixubis] is proven when used according to FDA labeled indications. Both of the following criteria must be met:\textsuperscript{19,34-36,46}

a. Diagnosis of hemophilia B
b. One of the following:
   (1) Control and prevention of bleeding episode
   -OR-
   (2) Prevention of bleeding in surgical interventions (i.e., surgical prophylaxis)

3. Anti-Inhibitor Coagulant Complex (plasma-derived) [FEIBA NF, FEIBA VH] and Factor VIIa (recombinant) [NovoSeven, NovoSeven RT] are proven when used according to FDA labeled indications. All of the following criteria must be met:5,14,20,21,47
   a. Diagnosis of hemophilia B
   -AND-
   b. Documentation of inhibitors (e.g., Bethesda inhibitor assay)
   -AND-
   c. One of the following:
      (1) Treatment of a spontaneous bleeding episode
      -OR-
      (2) Prevention of bleeding in surgical interventions (i.e., surgical prophylaxis)
      -OR-
      (3) Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

F. Fibrinogen Deficiency (i.e., Factor I deficiency)
   1. Fibrinogen Concentrate (plasma-derived) [RiaSTAP] is proven when used according to FDA labeled indications. All of the following criteria must be met:43
      a. Diagnosis of congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
      -AND-
      b. Treatment of acute bleeding episode

*Additional information to support medical necessity review where applicable:
The above indications and criteria apply to medical necessity review.

Centers for Medicare and Medicaid Services (CMS):
In general, Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf.

Medicare does have a National Coverage Determination (NCD) for Anti-Inhibitor coagulation complex (AICC). Refer to the NCD for Anti-Inhibitor Coagulant Complex (AICC) (110.3). Local Coverage Determinations (LCDs) do exist. Refer to the LCDs for Hemophilia Clotting Factors and Hemophilia Factor Products.

(Accessed November 21, 2013)
BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

Additional Information: Clinical coverage in this policy addresses the drug only. It does not address coverage for home health care including nursing services. These products may be a covered service on the pharmacy benefit. Please refer to the enrollee-specific benefit document.

The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

BACKGROUND

Factor VIIa (FVIIa) is a vitamin K-dependent glycoprotein made up of 406 amino acid residues, and is structurally similar to human plasma-derived factor VIIa. FVIIa promotes hemostasis by forming complexes with tissue factor and activating coagulation factors in the intrinsic pathway: factor X to factor Xa, and factor IX to factor IXa. Activated factor X, complexed with other factors, converts prothrombin to thrombin and fibrinogen to fibrin to form a hemostatic plug.5,32

Factor XIII (FXIII) is a naturally occurring glycoprotein in plasma that promotes cross-linking of fibrin during the coagulation process, and protects the newly formed clot from fibrinolysis. FXIII is a proenzyme which is activated in the presence of calcium ion, to form activated factor XIIIa. The activated form is homodimeric, with only the A-subunit having intracellular activity. The B-subunit has no enzymatic activity and functions to stabilize the structure against proteolysis.1,32

Coagulation factor XIII A-subunit is a recombinant human factor XIII-A(2) homodimer composed of 2 factor XIII A-subunits. Recombinant coagulation factor XIII A-subunit binds to free human factor XIII B-subunit and is activated by thrombin in the presence of calcium. Once activated, it increases the mechanical strength of fibrin clots, retards fibrinolysis, and enhances platelet adhesion to the site of injury in a dose-dependent manner.51,32

Antihemophilic Factor VIII (FVIII) is a dried concentrate of Factor VIII derived from pooled human plasma. FVIII is the coagulant portion of the Factor VIII complex in plasma. FVIII acts as a cofactor for Factor IX to activate Factor X, ultimately causing the formation of thrombin and fibrin, promoting platelet aggregation and adhesion to damaged vascular endothelium.7,8,32

Antihemophilic Factor VIII / von Willebrand Factor Complex (human) is a lyophilized concentrate of factor VIII and von Willebrand Factor, which facilitates the activation of factor X ultimately causing the formation of thrombin and fibrin promoting platelet aggregation and adhesion to damaged vascular endothelium.2,4,32

Recombinant antihemophilic Factor VIII is not derived from human blood. It is a lyophilized preparation of factor VIII, which facilitates the activation of factor X ultimately causing the
formation of thrombin and fibrin promoting platelet aggregation and adhesion to damaged vascular endothelium.\textsuperscript{9-13,32,50}

All forms of factor IX (FIX) achieve hemostasis through the same mechanism. A complex of factor VII and tissue factor (via the extrinsic coagulation pathway) and factor Xla (via the intrinsic pathway) activate factor IX which, in combination with factor VIII:C, activates factor X to Xa. Through this pathway, prothrombin is converted to thrombin which, in turn, converts fibrinogen to fibrin clot.\textsuperscript{15-19,32}

The exact mechanism of action of anti-inhibitor complex (AICC) is unknown. It may be related to one or more of the active clotting factors and their ability to bypass the factor VIII inhibitor. In vitro experiments suggest the possibility of a factor Xa–like substance; or a complex of FVIIIC:Ag, factor IXa, and phospholipid as the active principle, which is only minimally inhibited by an inhibitor.\textsuperscript{14,32}

Fibrinogen (coagulation factor I) is a soluble plasma glycoprotein and a physiological substrate of 3 enzymes: thrombin, factor XIIIa, and plasmin. Thrombin converts fibrinogen into fibrin. Fibrin is stabilized in the presence of calcium ions and by activated Factor XIII. Factor XIIIa induces cross-linking of fibrin polymers which result in the fibrin clot being more elastic and more resistant to fibrinolysis. The cross-linked fibrin is the end result of the coagulation cascade. Cross-linked fibrin is the end result of the coagulation cascade, and provides tensile strength to a primary hemostatic platelet plug and structure to the vessel wall.\textsuperscript{32,43}

**CLINICAL EVIDENCE**

**PROVEN:**

**Congenital Factor XIII Deficiency:**

In a multinational, open-label, single-arm, phase 3 trial, researchers evaluated the efficacy and safety of prophylactic treatment with recombinant FXIII (rFXIII) [Treten] in congenital FXIII-A subunit deficiency.\textsuperscript{25,51} Forty-one patients ≥ 6 years of age (mean, 26.4; range, 7-60) with confirmed congenital FXIII-A subunit deficiency were enrolled into the trial which consisted of a 4-week run-in period, followed by a 52-week treatment period (visits 2-15) of monthly (28 ± 2 days) IV doses of 35 IU/kg of rFXIII. During the rFXIII treatment period, 5 bleeding episodes (all trauma induced) in 4 patients were treated with FXIII-containing products. Crude mean bleeding rate was significantly lower than the historic bleeding rate (0.138 vs 2.91 bleeds/patient/year, respectively) for on-demand treatment. Transient, non-neutralizing, low-titer anti-rFXIII antibodies (Abs) developed in 4 patients; however, this did not result in allergic reactions, changes in any bleeds requiring treatment, or changes in FXIII pharmacokinetics during the trial or follow-up. These non-neutralizing Abs declined below detection limits in all 4 patients despite further exposure to rFXIII or other FXIII-containing products. Researchers conclude that prophylactic treatment with rFXIII is safe and effective in preventing bleeding episodes in patients with congenital FXIII-A subunit deficiency.

Factor XIII concentrate (human) [Corifact] labeling included expanded information in regards to use of rFXIII for peri-operative treatment of bleeds.\textsuperscript{1} Out of the 41 patients included in the trial, 5 patients underwent surgical procedures (4 were elective and 1 was an emergency). Of the 4 elective surgeries, 3 patients received rFXIII prior to surgery (0 to 7 days prior to surgery) with no post-operative bleeding. One patient who received rFXIII 7 days prior to surgery experienced bleeding post-extraction of all four wisdom teeth. The bleeding was stopped four hours after the oral surgery with an additional dose of rFXIII (50% of the patient's routine dose). One patient who required emergency surgery was pre-treated with plasma.
Von Willebrand Disease (VWD):
Gill et al. conducted a prospective, open-label, multinational study which evaluated the safety, efficacy and optimal dosing of a VWF/FVIII concentrate [Humate-P] in patients with von Willebrand disease (VWD) undergoing elective surgery and expected to require at least two consecutive days of perioperative treatment with a VWF/FVIII concentrate. Dosing of factor was based on VWF ristocetin cofactor (VWF:RCo) and FVIII pharmacokinetic assessments performed before surgery. The studied population was composed of 33 adults and 9 children who completed the PK infusion phase. Effective haemostasis was achieved in 91.4% (32/35) of subjects immediately after surgery. Reported median terminal VWF:RCo half-life was 11.7 h, and median incremental in vivo recovery was 2.4 IU dL(-1) per IU kg(-1) infused. Three patients developed major hemorrhage after the immediate postoperative period. Median VWF/FVIII concentrate loading doses ranged from 42.6 IU VWF:RCo kg(-1) (oral surgery) to 61.2 IU VWF:RCo kg(-1) (major surgery), with a median of 10 (range, 2-55) doses administered per patient. Eleven patients experienced a total of 25 postoperative bleeding events, most of which were categorized as mild (16) or moderate (8). Researchers conclude that the results of this trial indicate that this VWF/FVIII concentrate is safe and effective in the prevention of excessive bleeding during and after surgery in individuals with VWD.

Researchers conducted a prospective, open-label, multicenter, non-randomized study which evaluated the safety and efficacy of a factor VIII (FVIII)/VWF concentrate [Humate-P] when used in treatment regimens based on VWF:ristocetin cofactor (VWF:RCo) activity in subjects with VWD in which desmopressin was known or suspected to be inadequate in situations requiring urgent and necessary surgery. Thirty-nine eligible patients with 42 evaluable surgical treatment events were included. Researchers reported the median loading dose based upon VWF:RCo activity was 82.3 international units/kilogram (IU kg(-1); range 32.5-216.8 IU kg(-1)), and the median maintenance dose per infusion was 52.8 IU kg(-1) (range 24.2-196.5 IU kg(-1)) for a median of 3 days (range 1-50 days). The median number of infusions per event was 6 (range 1-67 infusions). A total of 55 adverse events (AEs) were reported in 24 (57.1%) of 42 surgical treatment events and 3 of those AE events (which included peripheral edema, extremity pain and pseudothrombocytopenia) were reported as potentially treatment-related. No serious drug-related AEs or thrombotic events were reported. Researchers concluded that this study supports the safety and efficacy of treatment with FVIII/VWF concentrate for the prevention of surgical haemorrhage in patients with VWD when administered in doses calculated in VWF:RCo units.

Forty-five patients with von Willebrand disease (VWD) who received on demand von Willebrand factor/coagulation factor VIII complex (human) [Wilate] were evaluated in prospective clinical trials. bleeding was successfully controlled in 84.1% (95% confidence interval (CI), 81.8% to 86.2%) of episodes (898 of 1068 episodes); additionally, bleeding was successfully controlled in 93% of episodes in the 25 patients with VWD type 3. Non-successful treatment of a bleeding episode was documented if any of the following criteria was met: 1) the episodes was also treated with another VWF-containing product (excluding whole blood); 2) the patient required a blood transfusion during the bleeding episode; 3) the daily dosage of FVIII/VWF complex was 50% or greater above the initial required dose during follow-up treatment (for bleeding episodes requiring more than one day of treatment); 4) except for cases of gastrointestinal bleeding, FVIII/VWF complex was required for more than 4 days for the treatment of severe bleeding, more than 3 days for the treatment of moderate bleeding, or more than 2 days for the treatment of minor bleeding; and 5) the final bleeding episode had a moderate or none efficacy rating. Overall, most bleeding episodes were treated with FVIII/VWF complex for 1 to 3 days; however, patients with gastrointestinal bleeding the duration could be up to 7 days.
Congenital Factor VII Deficiency, Acquired Factor VIII Deficiency, Hemophilia A with Inhibitors, and Hemophilia B with Inhibitors:

Mariani et al conducted a multi-center, prospective, observational, web-based study protocol to collect and describe treatment modalities and outcomes in congenital FVII deficiency (STER [Seven Treatment Evaluation Registry]). Forty-one surgical operations (24 'major' and 17 'minor') were performed in 34 patients diagnosed with FVII deficiency and administered recombinant activated Factor VII (rFVIIa) [NovoSeven]. Bleeding occurred during three major interventions of orthopedic surgery; however, rFVIIa was administered at very low dose in each case. An antibody to FVII was observed in one patient who underwent multiple dental extractions. No thromboses were reported during the 30-d follow up period. Replacement therapy with rFVIIa for surgery in FVII deficient patients is effective and safe when minimally effective doses were used, which, during the period of maximum bleeding risk (the day of operation), was calculated (Receiver Operate Characteristic analysis) to be of at least 13 μg/kg/body weight per single dose and no less than three administrations.

Recombinant coagulation factor VIIa (rFVIIa) [NovoSeven RT] was found to be effective and well-tolerated for acute bleeding or hemostasis during surgery in patients diagnosed with one of the following: hemophilia with inhibitors, acquired inhibitors, or factor VII deficiency. In an open-label, multi-center study, patients with hemophilia with inhibitors (n=19), acquired inhibitors to factor VIII (n=4), or factor VII deficiency (n=5) were administered rFVIIa for either life- or limb-threatening bleeding episodes or for coverage during surgery. For episodic bleeding, dosing of rFVIIa was 90 micrograms/kilogram (mcg/kg) every 2 hours and the dose increased to 120 mcg/kg if no improvement was observed. During controlled bleeding, dosing intervals increased to 3 or more hours. Surgical procedure dosing of rFVIIa was 90 mcg/kg given immediately before surgery and repeated at 2 to 3 hour intervals for 24 to 48 hours. Dosing with rFVIIa continued for up to 2 weeks at increased intervals as needed. Factor VII deficient patients received rFVIIa 15 to 30 mcg/kg every 4 to 6 hours for bleeding or surgery. There were 67 treatment episodes evaluated. Researchers reported the following: mean treatment duration was 8.1 days (range 1 to 39 days); mean number of injections per treatment episode was 43 (range 1 to 142); and mean dose used was 25 mcg/kg for factor VII deficient patients and 90 mcg/kg for all other patients. Reported outcomes showed that rFVIIa was effective or partially effective in 85% of the bleeding episodes. During surgery, bleeding occurrence was at least equivalent to normal in 91% of procedures and in 91%, there was minimal or no oozing. Reported adverse events included thrombophlebitis in 3 patients, and fever in 2 patients.

Lusher et al. conducted a randomized, double-blind, parallel group, international multicenter trial which compared the efficacy of two dosage regimens of rFVIIa (given intravenously at periodic intervals) in the treatment of joint, muscle and mucocutaneous hemorrhages in persons with hemophilia A and B with and without inhibitors. Patients were randomized to one of the following treatments: Group A: 35 µg kg⁻¹ or Group B: 70 µg kg⁻¹, in blocks of 2. Within each block, one patient was assigned to the 35 µg kg⁻¹ dosing regimen and the other to 70 µg kg⁻¹ dose. One hundred sixteen patient had a baseline assessment for inclusion into the trial. Of these, 84 patients were treated on the protocol and 32 patients were not treated in the study, in most cases because they did not return to the clinic with an eligible bleeding episode. One hundred and seventy-nine bleeding episodes were treated, of which 145 (81%) were acute haemarthroses. Both treatments were efficacious, with 71% having an excellent (59% and 60%) or effective (12% and 11%) response. Overall, the mean and median number of doses given per episode of joint bleeding was 3.1 and 2, respectively. The mean number of doses was 3.1 for the 70 µg kg⁻¹ group and 2.7 for the 35 µg kg⁻¹ group (P value = 0.142). Researchers concluded that rFVIIa in a dosage of 35 µg kg⁻¹ or 70 µg kg⁻¹ is both safe and reasonably effective in the treatment of joint or muscle hemorrhages in hemophilic patients with inhibitor antibodies to factor
VIII or factor IX and that the appropriate dose for the treatment of joint and peripheral muscle bleeding is 35-70 µg kg⁻¹ given at 2-3 h intervals until hemostasis is achieved.

Researchers conducted a multicenter study which evaluated the efficacy of anti-inhibitor coagulant complex [FEIBA] in the treatment of joint, mucous membrane, musculoscutaneous and emergency bleeding episodes such as central nervous system hemorrhages and surgical bleedings. Of the 49 patients enrolled in the study, 44 patients had a diagnosis of hemophilia A with inhibitors, 3 patients had a diagnosis of hemophilia B with inhibitors, and 2 patients were diagnosed with acquired FVIII inhibitor. Forty-nine patients with inhibitor titers > 5 Bethesda Units were given 489 single doses for the treatment of 165 bleeding episodes. The usual dosage was 50 Units per kg of body weight which was repeated at 12-hour intervals (6-hour intervals in mucous membrane bleedings), if necessary. Researchers reported that bleeding was controlled in 153 episodes (93%), and in 130 (78%) of the episodes, hemostasis was achieved with one or more infusions within 36 hours (36% were controlled with one infusion within 12 hours). An additional 14% of episodes responded after more than 36 hours. Of the 489 single doses administered, 3.7% caused minor transient reactions in recipients. Researchers reported that 10 patients (20%) showed a rise in their inhibitor titers, and in 5 of these patients (10%), the rise was tenfold or more. Researchers concluded that anti-inhibitor coagulant complex appears to be safe and efficacious in the treatment of bleeding episodes with Factor VIII or Factor IX deficiencies with inhibitors.

Hemophilia A:
Three multi-center, open-label, non-controlled trials (n=213) were conducted to evaluate the safety and efficacy of antihemophilic factor (recombinant) [Novoeight] in the control and prevention of breakthrough bleeds, routine prophylaxis and perioperative management in previously treated patients with hemophilia A. Of the 213 patients included, 150 patients were 12 years or older and 63 patients were younger than 12 years of age with severe hemophilia A (factor VIII activity less than 1%) and no history of factor VIII inhibitors. The median annual bleeding rate for adults and children 16 years or older was 3.1 bleeds/year. All patients received routine prophylaxis with antihemophilic factor (recombinant); those 12 years or older received 20 to 50 international units/kg 3 times weekly or 20 to 40 international units/kg every other day. Those younger than 12 years of age received either 25 to 60 international units/kg 3 times weekly or 25 to 50 international units/kg every other day. More than 80% received the 3-times-per-week regimen. Bleeding episodes were treated according to the investigator's discretion, with a target factor VIII activity level greater than 0.5 international units/mL. Bleeding episodes and perioperative management with antihemophilic factor (recombinant) were considered successfully treated if the patient (home dosing) or investigator (supervised treatment) rated the response to treatment as excellent or good; moderate or none ratings were considered unsuccessful treatment. Bleeding episodes (89% mild/moderate; 62% spontaneous; 72% localized to joints) occurred 991 times in 158 patients, with 84% successfully treated and 1.7% having no response. Only 1 or 2 injections were necessary to treat 91% of the bleeding episodes. Of the 11 patients (age range, 14 to 55 years) undergoing surgical procedures, 10 of the procedures were major (tooth extraction). Excellent or good efficacy ratings were given in all cases.

Valentino et al. conducted an open-label, multicenter trial which compared the effectiveness of two prophylactic treatment regimens with antihemophilic factor (recombinant), plasma/albumin free method (rAHF-PFM) [Advate], as well as between on-demand and prophylaxis treatments, in preventing bleeding in hemophilia A. Thirty-six previously on-demand-treated patients aged 7-59 years with FVIII levels ≤ 2% received 6 months of on-demand treatment and were then randomized to 12 months of either standard (20-40 IU kg⁻¹ every other day) or pharmacokinetic (PK)-tailored (20-80 IU kg⁻¹ every third day) prophylaxis, both regimens intended to maintain FVIII trough levels at or above 1%. The primary endpoint was differences in annualized bleeding.
rates (ABRs) between the two prophylaxis regimens. Secondary endpoint evaluated included differences in ABRs between patients first treated on-demand and then on prophylaxis. A total of 1640 bleeding episodes occurred in 66 of 66 subjects during the on-demand period, 104 episodes occurred in 19 out of 32 subjects during standard prophylaxis and 141 episodes in 25 out of 34 subjects during the PK-tailored prophylaxis. Twenty-two (33.3%) patients on prophylaxis treatment experienced no bleeding episodes, whereas none treated on-demand were free from an episode of bleeding. ABRs for the two prophylaxis regimens were comparable, however, the differences between on-demand and either prophylaxis were statistically significant (p <0.0001): median (interquartile range [IQR]) ABRs were 43.9 (21.9), 1.0 (3.5), 2.0 (6.9) and 1.1 (4.9) during on-demand treatment, standard, PK-tailored and any prophylaxis, respectively. No differences in FVIII consumption or adverse event rates between prophylaxis regimens were noted. No patient developed FVIII inhibitors. Researchers concluded that the outcomes of this trial demonstrated comparable safety and effectiveness for two prophylaxis regimens and that prophylaxis significantly reduces bleeding compared with on-demand treatment. Additionally, PK-tailored prophylaxis offers an alternative to standard prophylaxis for the prevention of bleeding in hemophilia A.

Tarantino et al. evaluated the efficacy, safety, pharmacokinetics and immunogenicity of antihemophilic factor (recombinant) produced by the plasma, albumin-free method (rAHF-PFM) in 111 previously treated patients diagnosed with hemophilia A.38 The study comprised a randomized, double-blinded, crossover pharmacokinetic comparison of rAHF-PFM and rAHF (R-FVIII) [Recombinate]; prophylaxis (three to four times per week with 25-40 IU kg(-1) rAHF-PFM) for at least 75 exposure days; and on-demand treatment of episodic hemorrhagic events. Median age was 18 years, 96% of subjects had baseline factor VIII <1%, and 108 patients received at least one infusion of study drug. Bioequivalence, based on area under the plasma concentration vs. time curve and adjusted in vivo recovery, was demonstrated for rAHF-PFM and R-FVIII in both per-protocol and intent-to-treat data sets. Mean (±SD) half-life for rAHF-PFM was 12.0 ± 4.3 h. Among 510 bleeding events treated, 473 (93%) were managed with one or two infusions of rAHF-PFM and 439 (86%) had efficacy ratings of excellent or good. Patients who were less adherent to the prophylactic regimen had a higher bleeding rate (9.9 episodes subject(-1) year(-1)) than subjects who were more adherent (4.4 episodes subject(-1) year(-1); p<0.03). A total of 877 adverse events were reported by 101 of the 108 patients who received treatment with at least one study drug infusion. The majority of adverse events appeared to be related to trauma, intercurrent mild respiratory disease, or complications of hemophilia. Ten (1%) events in six of the patients were serious, however, none were related to rAHF-PFM and none resulted in death or serious sequelae. One patient developed a low titre, non-persistent inhibitor (2.0 BU) after 26 exposure days. Researchers concluded that the outcomes of the trial demonstrated that rAHF-PFM is bioequivalent to R-FVIII, and suggest that rAHF-PFM is efficacious and safe, without increased immunogenicity, for the treatment of hemophilia A.

Manco-Johnson et al. conducted a multicenter, randomized, open-label trial evaluating whether prophylactic factor VIII infusions, given every other day, are more effective in preventing joint damage than an intensive replacement regimen given at the time of a hemarthrosis.44 Sixty-five boys younger than 30 months of age with severe hemophilia A were randomized to prophylactic infusions of recombinant factor VIII (n=32) or to an enhanced episodic infusion schedule of at least three doses totaling a minimum of 80 IU of factor VIII per kilogram of body weight at the time of a joint hemorrhage (n=33). The primary endpoint was preservation of index-joint structure, as determined by means of magnetic resonance imaging (MRI) and plain-film radiography at the completion of the study, when participants were 6 years old. Secondary outcomes measured were number of joint and other bleeding events, number of infusions, and total units of factor VIII administered. At 6 years of age, researchers reported that 93% of those in the prophylaxis group and 55% of those in the episodic-therapy group were considered to have normal index-joint structure. Researchers concluded that prophylactic factor VIII infusions, given every other day, are more effective in preventing joint damage than an intensive replacement regimen given at the time of a hemarthrosis.
structure on MRI \( (p=0.006) \). The relative risk of MRI-detected joint damage with episodic therapy as compared with prophylaxis was 6.1 (95% confidence interval, 1.5 to 24.4). The mean annual numbers of joint and total hemorrhages were higher at study exit in the episodic-therapy group than in the prophylaxis group \( (p<0.001 \text{ for both comparisons}) \). High titers of inhibitors of factor VIII developed in two boys who received prophylaxis; three boys in the episodic-therapy group had a life-threatening hemorrhage. Hospitalizations and infections associated with central-catheter placement did not differ significantly between the two groups. Researchers concluded that prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A.

Löfqvist et al. evaluated the use of long-term prophylactic factor treatment in young patients with severe hemophilia A and B on orthopedic and radiological outcomes.\(^{37}\) In a 5-year follow-up evaluation of 60 patients aged 2 to 25 years with hemophilia (severe hemophilia, \( n=34 \); hemophilia A, \( n=29 \); hemophilia B, \( n=5 \)), doses of factor ranged from 25 to 40 units/kilogram body weight (U/kg) three times weekly for hemophilia A and twice weekly for hemophilia B. The aim was to maintain factor levels above 1% of normal between infusions. Orthopedic and radiological joint scores were evaluated according to recommendations by the World Federation of Haemophilia. Results of the trial showed that orthopedic and radiological joint scores were found to have remained unchanged during follow-up in almost all patients and to be still zero (i.e. no unaffected joints) in 79% \( (n=27) \) of the patients. Authors concluded that results of the study support the consensus that hemophilic arthropathy can be prevented by administering early high-dose prophylaxis.

**Hemophilia B:**

In a prospective, open-label, uncontrolled trial, efficacy of routine prophylaxis with coagulation factor IX [Rixubis] in adult patients with hemophilia B \( (n=56) \) was evaluated. Primary endpoint was reduction in frequency of bleeding episodes. Patients received coagulation factor IX recombinant 40 to 60 international units/kg IV twice weekly for 3 months or longer. At screening, all patients had severe (factor IX level < 1%) or moderately severe (factor IX level \( \leq \) 2%) hemophilia B, with 12 or more documented bleeding episodes requiring treatment within 12 months prior to enrollment. After a mean duration of 6 months of treatment with coagulation factor IX recombinant at a mean twice-weekly dose of 49.4 international units/kg/infusion, the mean total annualized bleeding rate was 4.3 for all bleeds, 1.7 for spontaneous bleeds, and 2.9 for joint bleeds compared with 33.9 +/- 17.37 mean total annualized bleeding rate in the on-demand arm \( (n=14) \) during the mean 3.5-month period.\(^{46}\)

Shapiro et al, conducted an international, multicenter, open-label, single-cohort study which evaluated the safety and efficacy of recombinant factor IX [rFIX] [BeneFIX] in previously untreated patients (PUPS) with severe or moderately severe hemophilia B (FIX activity, \( < \text{ or } = 3 \) IU/dL).\(^{34}\) Sixty-seven PUPS were enrolled in the study, but only 63 PUPS aged younger than 1 month to 14 years received rFIX (median treatment duration, 37 months; range, 4-64 months). On day 1, rFIX was administered in the clinic by intravenous infusion for rFIX recovery and 24-hour survival. For assessments of recovery and survival, plasma rFIX activity was measured prior to rFIX infusion, as soon as possible after infusion (preferably within 30 minutes of infusion), and 4 and 24 hours after infusion. rFIX was administered at a dose of 50 IU/kg for recovery and 24-hour survival assessments if the patient was in a nonbleeding state. Thereafter, rFIX was administered for on-demand treatment of any bleeding episode at a dose deemed appropriate or as a prophylactic treatment to prevent either hemorrhage or surgery-related bleeding. Researchers reported that the mean rFIX recovery \( (0.68 \pm 0.27 \text{ IU/dL per IU/kg}) \) remained constant over 5 years and was similar in infants (1 month to < 2 years) and children (2 to < 12 years). Fifty-four PUPS used rFIX (median dose, 62.7 IU/kg per infusion; range, 8.2-292 IU/kg) to
treat 997 hemorrhages. Bleeding was well controlled with rFIX treatment, and 75% of hemorrhages requiring only one rFIX infusion. Reported response to rFIX was "excellent" or "good" in 94% of cases. Effective hemostasis was achieved in 32 PUPs receiving rFIX for routine prophylaxis, with 91% of prophylaxis responses rated "excellent." rFIX administered for 30 surgical procedures in 23 PUPs achieved hemostasis for all rated procedures. Five patients experienced allergic-type reactions, including 2 (3%) patients who developed FIX inhibitors (both > 5 BU/dl). rFIX was well tolerated, with no associated thrombotic events or evidence of viral transmission. Researchers concluded that the outcomes of this study indicate that rFIX is a safe and effective treatment for PUPs with hemophilia B.

To assess safety and efficacy of recombinant factor IX (fFIX) [BeneFix] in patients undergoing major or minor surgery, researchers conducted an open-label observational study of 28 patients undergoing 34 surgical procedures. The study population included patients with severe (17), moderate (6), and mild (3) hemophilia B, and 2 female hemophilia B carriers; median age was 36 (range, 3 to 69 years). rFIX was administered as a preoperative intravenous bolus at a dose determined on an individual basis by the investigator with amounts that ranged from 25 international units/kilogram (IU/kg) to 155 IU/kg. The average continuous rFIX infusion dose was 6.4 IU/kg/hour (hr) (range 4.3 to 8.6 IU/kg/hr) and mean infusions days was 4.9 (range 1 to 11 days). Blood loss during and after the procedure was similar to that expected in non-hemophilic patients; it ranged from 0 to 1500 mL intraoperatively and from 0 to 2676 mL postoperatively. Perioperative transfusions were required by 3 patients, including 1 liver transplant patient. Physicians rated the preoperative response to rFIX as excellent (83%) or good (17%), and postoperatively as excellent (78%) or good (22%). Additionally, there were no reports of spontaneous hemorrhage. Patient ratings of rFIX were excellent (63%) or good (36%). Adverse events occurred in 15 of 28 (53.6%) patients, but none were perioperative hemorrhages, thromboembolic events, coagulation activation, viral transmission, or inhibitor formation. One patient developed a preoperative transient low-responding FIX inhibitor, but no change in treatment was required and it resolved 15 months later. Four subjects experienced 1 or more adverse events, including rash, flushing, headache, sneezing, dry cough, or local phlebitis. One patient developed an episode of hives. Researchers conclude that rFIX was found to be safe and effective in achieving hemostasis in subjects with FIX deficiency undergoing surgery.

Researchers conducted a multicenter study to evaluate safety and efficacy of recombinant human factor IX (rFIX) in previously treated (with high-purity, monoclonal antibody-purified plasma-derived factor IX (pdFIX)) patients with severe or moderate hemophilia B for the treatment or prevention of bleeding episodes. Fifty-five eligible patients completed the study and median time on study was 741 days; total infusions were 7362, resulting in a cumulative total of 20,923,634 IU of rFIX infused. A mean incremental factor IX recovery was reported as 0.75 IU/dL per IU/kilogram (kg) (30% lower than expected for pdFIX) with a corresponding mean recovery of 33.7% (range 15.3% to 62.2%); a tendency for lower recovery was observed in younger patients. All on-demand hemorrhages were controlled by rFIX with a median dose of 42.8 IU/kg and most hemorrhage (80.9%) episodes were controlled with one rFIX infusion. Forty-seven subjects used rFIX on a prophylactic basis with a median dose of 35.1 IU/kg and 93% of them were rated as excellent or effective. Researchers reported that rFIX infusions given prior to surgical procedures were rated as providing excellent or good hemostasis 98% of the time. There was no evidence of transmission of hepatitis A, B, or C nor HIV1 or HIV2. One patient exhibited evidence of a low-titer, transient factor IX inhibitor which resolved spontaneously. Four cases of minor allergic reactions (tests for antifactor IX IgE were negative) were reported, and other adverse side effects were similar to those experienced with pdFIX. Researchers conclude that rFIX was found to be safe and effective for prevention of bleeding in patients with hemophilia B who were followed for 2 years after initiation of the medication despite a lower recovery compared with pdFIX. It may provide a safe advantage in terms of risk from blood-borne pathogens.

Hemophilia Policy: Clotting Factors and Coagulant Blood Products (Effective 06/01/2014)
Two studies were conducted to provide coagulation factor IX (human) [Mononine] for treatment of hemophilia B subjects who required extensive Factor IX replacement for surgery, trauma, or spontaneous bleeding (73 unique subjects and eight subjects enrolled twice for a total of 81 subjects), as well as to evaluate the safety and efficacy of coagulation factor IX (human) treatment.\(^\text{17}\) The overall mean recovery during treatment was determined to be 1.23 ± 0.42 IU/dL rise/IU/kg (K) (range = 0.59 to 2.92 K) among the 55 subjects included in recovery analyses in Study 1 and to be 1.12 ± 0.52 K (range = 0.61 to 2.08 K) among 10 subjects included in these analyses in Study 2. Five (5/81,6\%) subjects reported adverse events attributed to coagulation factor IX (human) across both studies. In these studies, 100 doses of coagulation factor IX (human) were administered at a range of 71 to 161 IU/kg to a total of 36 subjects. Sixty-seven of these infusions were the subject of recovery analyses. Mean recovery tended to decrease as the dose of coagulation factor IX (human) increased: 1.09 ± 0.52 K at doses > 75-95 IU/kg (n=38), 0.98 ± 0.45 K at doses > 95-115 IU/kg (n=21), 0.70 ± 0.38 K at doses > 115-135 IU/kg (n=2), 0.67 K at doses > 135-155 IU/kg (n=1), and 0.73 ± 0.34 K at doses > 155 IU/kg (n=5). Among the 36 subjects who received these high doses, only one (2.8\%) reported an adverse experience with a possible relationship to coagulation factor IX (human). No thrombogenic complications were observed or reported.

**Fibrinogen Deficiency:**

Kreuz et al evaluated the efficacy and tolerability of pasteurized human fibrinogen concentrate in an open, multi-center, non-controlled retrospective study in 12 patients with congenital fibrinogen deficiency.\(^\text{45}\) Hemostatic efficacy was assessed by laboratory investigation and clinical observation. The study included the following patient breakdown: afibrinogenemia (n=8); hypofibrinogenemia, (n=3); and dysfibrinogenaemia combined with hypofibrinogenemia (n=1). Fibrinogen substitution was indicated: to stop an ongoing bleed; as prophylaxis before surgery; or for routine prophylaxis to prevent spontaneous bleeding. In total, 151 fibrinogen infusions were recorded. The median single dosage was 63.5mg/kg body weight for bleeding events or surgery and 76.9 mg/kg for prophylaxis. The median total dose per event for bleeding events or surgery was 105.6 mg/kg. Fibrinogen was administered in 26 bleeding episodes; 11 surgical operations; and 89 prophylactic infusions, of which 86 were received by one patient. The median response (n = 8) was 1.5 mg/dl per substituted mg of fibrinogen per kg body weight (0.8-2.3). The median in vivo recovery (n = 8) was 59.8\% (32.5-93.9). Researcher reported clinical efficacy as very good in all events with the exception of one surgical procedure, where it was moderate. No inter-current bleeding occurred during prophylaxis. All but one infusion was well tolerated; the patient, who was administered 86 prophylactic infusions, experienced an anaphylactic reaction after the 56th infusion. In addition, one patient developed deep vein thrombosis and non-fatal pulmonary embolism with treatment for osteosynthesis after collum femoris fracture. Fibrinogen substitution could not be excluded as a contributing factor in this high-risk patient. Researchers concluded that substitution with pasteurized human fibrinogen concentrate in patients with congenital fibrinogen deficiencies is efficient and generally well tolerated.

**Technology Assessments:**

The Cochrane Collaboration published a 2011 intervention review which evaluated the effectiveness of recombinant FVIIa concentrate in comparison to plasma-derived concentrates (high-dose human or recombinant FVIII or FIX concentrate; prothrombin complex concentrates (PCCs); activated prothrombin complex concentrate (aPCC)) for the treatment of acute bleeding episodes in people with hemophilia and inhibitors.\(^\text{23}\) Researchers concluded that although there is a need for further randomized controlled trials, both rFVIIa (NovoSeven\textsuperscript{©}) and aPCC (FEIBA\textsuperscript{©}) can be used to treat bleeding in hemophiliacs with inhibitors. Additionally, clinical trials did not show a difference in the effectiveness of the two products and both were equally safe in terms of tolerability and the absence of clotting complications.

*Hemophilia Policy: Clotting Factors and Coagulant Blood Products (Effective 06/01/2014)*

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The Cochrane Collaboration also published an intervention review which evaluated the effectiveness of clotting factor concentrate prophylaxis in the management of people with hemophilia A or B in 2011. Authors conclude that there is strong evidence from randomized controlled trials and observational trials that prophylaxis started early preserves joint function in children with hemophilia as compared to on-demand treatment. This effect is due to a consistent reduction in total bleeds and hemarthrosis and leads to a significant improvement in quality of life, however, treatment prophylaxis is linked to an increased factor usage and overall cost of therapy. There was insufficient evidence to show that treatment prophylaxis decreased bleeding and related complications in patients with existing joint damage. Randomized controlled trials are warranted to establish the best preventative regimen for these patients.

**Professional Societies:**
The World Federation of Hemophilia developed 2013 guidelines which provides practical guidelines on the general management of hemophilia (level 1 corresponding to the strongest evidence and level 5 the weakest) as outlined below:

- **Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function.** (Level 2) In patients with repeated bleeding, particularly into target joints, short-term prophylaxis for 4–8 weeks can be used to interrupt the bleeding cycle. This may be combined with intensive physiotherapy or synoviorthesis. (Level 3)
- **Prophylactic administration of clotting factor concentrates is advisable prior to engaging in activities with higher risk of injury.** (Level 4) Preoperative assessment should include inhibitor screening and inhibitor assay, particularly if the recovery of the replaced factor is significantly less than expected. (Level 4)
- **Patients with mild hemophilia A, as well as patients receiving intensive factor replacement for the first time, are at particular risk of inhibitor development and should be re-screened 4–12 weeks postoperatively.** (Level 4)
- **The WFH strongly recommends the use of viral-inactivated plasma-derived or recombinant concentrates in preference to cryoprecipitate or fresh frozen plasma (FFP) for the treatment of hemophilia and other inherited bleeding disorders.** (Level 5)
- **For treatment of FIX deficiency, a product containing only FIX is more appropriate than prothrombin complex concentrates, which also contain other clotting factors such as factors II, VII, and X, some of which may become activated during manufacture.** Products containing activated clotting factors may predispose to thromboembolism. (Level 2) Whenever possible, the use of pure FIX concentrates is preferable for the treatment of hemophilia B as opposed to PCC (Level 2)
- **Cryoprecipitate is preferable to FFP for the treatment of hemophilia A and VWD.** (Level 4) Due to concerns about the safety and quality of FFP, its use is not recommended, if avoidable. (Level 4)
- **DDAVP may be the treatment of choice for patients with mild or moderate hemophilia A when FVIII can be raised to an appropriate therapeutic level because it avoids the expense and potential hazards of using a clotting factor concentrate.** (Level 3) Although DDAVP is not licensed for use in pregnancy, there is evidence that it can be safely used during delivery and in the postpartum period in an otherwise normal pregnancy. Its use should be avoided in pre-eclampsia and eclampsia because of the already high levels of VWF. (Level 3)
- **Regular treatment with tranexamic acid alone is of no value in the prevention of hemarthroses in hemophilia.** (Level 4) It is valuable, however, in controlling bleeding from skin and mucosal surfaces (e.g., oral bleeding, epistaxis, menorrhagia). (Level 2)
Tranexamic acid is particularly valuable in the setting of dental surgery and may be used to control oral bleeding associated with eruption or shedding of teeth. (Level 4)

- Management of bleeding in patients with inhibitors must be in consultation with a center experienced in their management. (Level 5) Choice of treatment product should be based on titer of inhibitor, records of clinical response to product, and site and nature of bleed. (Level 4) Patients with a low-responding inhibitor may be treated with specific factor replacement at a much higher dose, if possible, to neutralize the inhibitor with excess factor activity and stop bleeding. (Level 4) Patients with a history of a high responding inhibitor but with low titers may be treated similarly in an emergency until an anamnestic response occurs, usually in 3–5 days, precluding further treatment with concentrates that only contain the missing factor. (Level 4)

In November 2012, the National Hemophilia Foundation (NHF) released updated hemophilia treatment guidelines entitled Medical and Scientific Advisory Council (MASAC) Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders #215. A summary of the NHF recommendations for physicians treating patients with hemophilia A and B, von Willebrand Disease, and other congenital bleeding disorders are as follows:

| Treatment of Patients with Hemophilia A |  |
|----------------------------------------|  |
| Recombinant Factor VIII Concentrates    | Advate                                |
|                                        | Helixate FS                           |
|                                        | Kogenate FS                           |
|                                        | Recombinate                           |
|                                        | Xyntha                                |
| Plasma-Derived Factor VIII Concentrates | Hemofil M                             |
|                                        | Monoclate-P                           |
| Cryoprecipitate                        | Cryoprecipitate                       |
| Desmopressin                           | DDAVP                                 |
|                                        | Stimate Nasal Spray for Bleeding      |

Treatment of choice in hemophilia A. Recommended for use in mild hemophilia A. Children < 2 years of age, pregnant women, and patients with mild hemophilia A in whom desmopressin does not provide adequate Factor VIII levels should be treated with either recombinant or plasma-derived FVIII concentrates.

| Treatment of Patients with Hemophilia B |  |
|----------------------------------------|  |
| Recombinant Factor IX Concentrate      | BeneFIX                              |
| Plasma-Derived Factor IX Concentrates  | AlphaNine SD                         |
|                                        | Mononine                             |

Treatment of choice in hemophilia B. Recommended

| Treatment of Patients with von Willebrand Disease (VWD) |  |
|--------------------------------------------------------|  |
| Desmopressin                                           | DDAVP                                |
|                                                        | Stimate Nasal Spray for Bleeding     |
| Plasma-Derived Factor VIII / von Willebrand            | Alphanate                            |

Recommended for most persons with VWD Type 1. Some Type 2A patients may respond to DDAVP, however clinical testing should be done to determine whether DDAVP can be used. Recommended in certain types of VWD that do not respond to DDAVP (i.e. Type
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<tr>
<th>Factor</th>
<th>Humate-P</th>
<th>Wilate</th>
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<tr>
<td>2B VWD and Type 3 VWD), and for use in Type 1 or 2A VWD patients who have become transiently unresponsive to DDAVP and in surgical situations, especially in young under the age of 2 years. In certain patients, Koate-DVI may also be effective.</td>
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<tr>
<th>Cryoprecipitate</th>
<th>Cryoprecipitate</th>
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<tr>
<td>Not recommended except in life- and limb-threatening emergencies when VWD-containing factor VIII concentrate is not immediately available.</td>
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### Treatment of Patients with Inhibitors to Factor VIII or IX

<table>
<thead>
<tr>
<th>Activated Prothrombin Complex Concentrate (aPCC)</th>
<th>FEIBA NF</th>
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<tr>
<td>Recommended, however, products are not interchangeable and are dependent on multiple factors including type of inhibitor (low- or high-responding), current titer of inhibitor, location of the bleed, and previous response to these products. Do not exceed recommended doses to reduce the risk of thrombosis.</td>
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<tr>
<th>Recombinant Factor VIIa Concentrate</th>
<th>NovoSeven RT</th>
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<tbody>
<tr>
<td>Treatment of Patients with Factor VII Deficiency</td>
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<tr>
<th>Recombinant Factor VIIa Concentrate</th>
<th>NovoSeven RT</th>
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<td>Recommended</td>
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### Treatment of Patients with Factor XIII Deficiency

<table>
<thead>
<tr>
<th>Plasma-derived Factor XIII Concentrate</th>
<th>Corifact</th>
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<tbody>
<tr>
<td>Recommended</td>
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### Treatment of Patients with Factor II or Factor X Deficiencies

<table>
<thead>
<tr>
<th>Plasma-Derived Prothrombin Complex Concentrates (pd-PCCs)</th>
<th>Bebulin</th>
<th>Profilnine SD</th>
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<tbody>
<tr>
<td>Recommended, however, it should be noted that these products vary in amount of factor content.</td>
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### Treatment of Patients with Factor I Deficiency

<table>
<thead>
<tr>
<th>Plasma-derived Fibrinogen Concentrate</th>
<th>RiaSTAP</th>
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</thead>
<tbody>
<tr>
<td>Recommended for treatment of congenital hypofibrinogenemia and afibrinogenemia but not dysfibrinogenemia</td>
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The American Society of Hematology released an updated reference guide entitled 2012 Clinical Practice Guideline on the Evaluation and Management of von Willebrand Disease (VWD) which provides a summary of the 2008 von Willebrand Disease (VWD): Evidence-based Diagnosis and Management Guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). A summary of the recommendations for the management of VWD is as follows:

- Therapeutic trial of DDAVP is recommended prior to use. VWF:RCo and FVIII activities should be measured at baseline and within 1 hour. Additional testing 2-4 hours after DDAVP should be considered to evaluate for shortened survival.
- Most type 1 VWD patients will respond to DDAVP, although patients with VWF:RCo <10 IU/dL and FVIII activity <20 IU/dL are less likely to have a clinically significant response. In type 2 VWD, DDAVP will increase the VWF concentration, but the VWF dysfunction will still be present. In type 2B VWD, DDAVP may result in transient thrombocytopenia. Therefore, DDAVP should be used with caution in type 2 VWD.
- To avoid tachyphylaxis, DDAVP therapy is typically discontinued after 2 or 3 daily doses.
- Minor bleeding should be treated with intravenous or nasal DDAVP, if results of a DDAVP trial support its use.
- In presence of inadequate DDAVP response, VWF concentrate should be used, with dosing primarily based on VWF:RCo units and secondarily on FVIII units.
- For patients with mild to moderate VWD undergoing oral surgery, antifibrinolytics combined with DDAVP are generally effective.
- For severe bleeding (e.g. intracranial, retroperitoneal) or major surgery prophylaxis, initial target VWF:RCo and Factor VIII activity levels should be >100 IU/dL, and levels >50 IU/dL should be maintained for at least 7-10 days. In all patients receiving VWF concentrate, clinicians should perform proper thrombotic-risk assessment and institute appropriate strategies to prevent thrombosis.

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Advate (antihemophilic factor (recombinant)) is approved by the U.S. Food and Drug Administration (FDA) for the following: control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A; perioperative management in adults and children (0-16 years) with hemophilia A; and routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children (0-16 years) with hemophilia A. Advate is not indicated for the treatment of von Willebrand disease.

Alphanate (antihemophilic factor/von Willebrand factor complex (human)) is FDA-labeled for control and prevention of bleeding in patients with hemophilia A or acquired Factor VIII deficiency. It is also approved for surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. Alphanate is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

AlphaNine SD (coagulation factor IX (human)) is FDA-labeled for the prevention and control of bleeding episodes 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 coumarin anticoagulant-induced hemorrhage, nor in the treatment of hemophilia A patients with inhibitors to Factor VIII.

Bebulin (factor IX complex) is FDA-labeled for the prevention and control of bleeding episodes in adult patients with hemophilia B. Bebulin is not indicated for use in the treatment of Factor VII deficiency.

BeneFIX (coagulation factor IX (recombinant)) is FDA-labeled for both control and prevention of bleeding episodes in adult and pediatric patients with hemophilia B, and for peri-operative management in adult and pediatric patients with hemophilia B.

Corifact (factor XIII concentrate (human)) is FDA-labeled for routine prophylactic treatment and peri-operative management of surgical bleeding in congenital Factor XIII deficiency.

FEIBA NF, FEIBA VH (anti-inhibitor coagulant complex) is FDA-labeled for the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and hemophilia B patients with inhibitors. It is also indicated for peri-operative management and routine prophylaxis to reduce the frequency of bleeding episodes in hemophilia A and B patients. FEIBA

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is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to factor VIII or factor IX.14,48

Helixate FS (antihemophilic factor (recombinant)) is FDA-labeled for the following: control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A; peri-operative management in adults and children with hemophilia A; and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no pre-existing joint damage. It is not indicated for the treatment of von Willebrand disease.10

Hemofil M (antihemophilic factor (human)) is FDA-labeled for the prevention and control of hemorrhagic episodes in hemophilia A. It is not indicated in von Willebrand disease.8

Humate-P (antihemophilic factor/von Willebrand factor complex (human)) is FDA-labeled for treatment and prevention of bleeding in adults with hemophilia A. It is also indicated in adults and children with von Willebrand disease (VWD) for treatment of spontaneous and trauma-induced bleeding episodes, and for prevention of excessive bleeding during and after surgery. This includes 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 in VWD.3

Koāte-DVI (antihemophilic factor (human)) is FDA-labeled for the treatment of hemophilia A in which there is a demonstrated deficiency of activity of the plasma clotting factor, factor VIII, to control or prevent bleeding episodes, or in order to perform emergency and elective surgery on individuals with hemophilia. Koāte-DVI is not approved for the treatment of von Willebrand's disease.7

Kogenate FS (antihemophilic factor (recombinant)) is FDA-labeled for the following: control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A; peri-operative management in adults and children with hemophilia A; and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no preexisting joint damage.11

Monoclate-P (antihemophilic factor (human)) is FDA-labeled for treatment of hemophilia A.

Mononine (coagulation factor IX (human)) is FDA-labeled for the prevention and control of bleeding in Factor IX deficiency, also known as hemophilia B or Christmas disease. It is not indicated in the treatment or prophylaxis of hemophilia A patients with inhibitors to Factor VIII.8

Novoeight (antihemophilic factor (recombinant)) is FDA-labeled for the control and prevention of bleeding episodes in adults and children with hemophilia A. It is also indicated for peri-operative management and routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A.50

NovoSeven, NovoSeven RT (coagulation factor VIIa (recombinant)) is FDA labeled for the following: treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia; prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors and in acquired hemophilia; treatment of bleeding episodes in congenital Factor VII (FVII) deficiency; and prevention of bleeding in surgical interventions or invasive procedures in congenital FVII deficiency.5,47
Profilnine SD (factor IX complex) is FDA-labeled for the prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. It is not indicated for use in the treatment of Factor VII deficiency.18

Recombinate (antihemophilic factor (recombinant)) is FDA-labeled for use in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes. It is also indicated in the perioperative management of patients with hemophilia A (classical hemophilia).12

RiaSTAP (fibrinogen concentrate (human)) is FDA-labeled for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.43

Rixubis (coagulation factor IX (recombinant)) is FDA-labeled for the control and prevention of bleeding episodes in adult patients with hemophilia B; for peri-operative management in adult patients with hemophilia B; routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with hemophilia B.46

Tretten (coagulation factor XIII A-Subunit (recombinant)) is FDA-labeled for routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency. It is not indicated for use in patients with congenital factor XIII B-subunit deficiency.51

Wilate (von Willebrand factor/coagulation factor VIII complex human)) is FDA-labeled 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. It is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients or for treatment of hemophilia A.4

Xyntha, Xyntha Solofuse (antihemophilic factor [recombinant], plasma/albumin-free) is FDA-labeled for control and prevention of bleeding episodes in patients with hemophilia A and for surgical prophylaxis in patients with hemophilia A. It is not indicated in patients with von Willebrand disease.13,49

**APPLICABLE CODES**

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J7178</td>
<td>Injection, human fibrinogen concentrate, 1 mg</td>
</tr>
<tr>
<td>J7180</td>
<td>Injection, factor XIII (antihemophilic factor, human), 1 IU</td>
</tr>
<tr>
<td>J7183</td>
<td>Injection, von Willebrand factor complex (human), Wilate, 1 IU vWF:RCo</td>
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<tr>
<td>J7185</td>
<td>Injection, factor VIII (antihemophilic factor, recombinant) (XYNTHA), per IU</td>
</tr>
<tr>
<td>J7186</td>
<td>Injection, antihemophilic factor VIII/von Willebrand factor complex (human), per factor VIII i.u.</td>
</tr>
<tr>
<td>J7187</td>
<td>Injection, von Willebrand factor complex (Humate-P), per IU VWF:RCO</td>
</tr>
</tbody>
</table>

Hemophilia Policy: Clotting Factors and Coagulant Blood Products (Effective 06/01/2014)

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Hemophilia Policy: Clotting Factors and Coagulant Blood Products (Effective 06/01/2014)

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>286.0</td>
<td>Congenital factor VIII disorder</td>
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<tr>
<td>286.1</td>
<td>Congenital factor IX disorder</td>
</tr>
<tr>
<td>286.3</td>
<td>Congenital deficiency of other clotting factors</td>
</tr>
<tr>
<td>286.4</td>
<td>von Willebrand's disease</td>
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<tr>
<td>286.52</td>
<td>Hemorrhagic disorder due to intrinsic circulating anticoagulants, antibodies or inhibitors; Acquired hemophilia</td>
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</table>

ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2014*, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.

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<th>ICD-10 Diagnosis Code (Effective 10/01/14)</th>
<th>Description</th>
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<tbody>
<tr>
<td>D66</td>
<td>Hereditary factor VIII deficiency</td>
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<tr>
<td>D67</td>
<td>Hereditary factor IX deficiency</td>
</tr>
<tr>
<td>D68.2</td>
<td>Hereditary deficiency of other clotting factors</td>
</tr>
<tr>
<td>D68.0</td>
<td>Von Willebrand's disease</td>
</tr>
<tr>
<td>D68.311</td>
<td>Acquired hemophilia</td>
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</tbody>
</table>

REFERENCES

Hemophilia Policy: Clotting Factors and Coagulant Blood Products (Effective 06/01/2014)


<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>10/1/2013</td>
<td>Updated policy to include Rixubis. Approved by National Pharmacy &amp; Therapeutics Committee on 8/20/13.</td>
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<tr>
<td>10/1/2013</td>
<td>New policy 2013D0047A. Approved by National Pharmacy &amp; Therapeutics Committee on 4/9/2013.</td>
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