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Subject: Clotting Factors and Coagulant Blood Products

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DESCRIPTION:

Hemostasis is regulated by a series of complex procoagulant and anticoagulant actions that involve the vessel wall, platelets, and the coagulation and fibrinolytic systems. An imbalance in any direction can result in coagulation disorders and specifically in a bleeding disorder when there is a deficiency of coagulation factors. Coagulation factor deficiencies present more frequently as an acquired deficiency such as disseminated intravascular coagulation (DIC) or vitamin K deficiency; inherited deficiencies are rarer, with the most common being deficiencies of factor VIII (hemophilia A) and factor IX (hemophilia B). Treatment of both acquired and inherited deficiencies involve factor replacement using either recombinant or purified plasma-derived products.

Rarely, individuals develop neutralizing antibodies, or inhibitors, to factor VIII and IX resulting in a decreased clinical response to factor replacement. Inhibitors are measured with the Bethesda assay with titers reported in Bethesda units (BU). One BU is the amount of inhibitor needed to inactivate half of factor VIII or IX in a mixture of normal and inhibitor-containing plasma. Patients with inhibitors are classified as either low responders (<5 BU/mL) or high responders (≥5 BU/mL). Administering high and more frequent doses of factor products may effectively manage bleeding episodes in low responders, while high responders should be managed with agents that bypass the factor to which the antibody is directed.

A brief overview of covered clotting factors and coagulant blood products is provided in Table 1.

TABLE 1

Review of clotting factor and coagulant blood products

Product	Notes
Anti-inhibitor Coagulant Complex *Feiba*	• Bypassing agent derived from human plasma • Contains factors II, VIIa, IX, and X • Labeled with units of factor VIII bypassing activity • Decreases activated partial thromboplastin time (aPTT) • Manufacturer suggests use as a first-line agent if inhibitor titer is greater than 10 BU/mL and second-line agent if inhibitor titer is 5-10 BU/mL • Inadequate response to treatment may result from an abnormal platelet count or impaired platelet function
Fibrinogen concentrate *Fibryga, RiaSTAP*	• Derived from human plasma • Factor I is a substrate for thrombin, factor XIIIa, and plasmin
Factor VIIa, recombinant *NovoSeven, NovoSeven RT, SevenFact*	• Bypassing agent generated from cloned human factor VII expressed in baby hamster kidney cells • Contains only activated factor VIIa • Short dosing interval (half-life: 3 hours)
Factor VIII Human: *Hemofil M, Monoclate-P* Recombinant: *Advate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha*	• Products differ based on purity and source of factor VIII • Facilitates the activation of factor X causing the formation of thrombin and fibrin • Factor VIII potency differs by product
Factor VIII/VWF complex *Alphanate, Humate P, Koate-DVI, Octanate, Wilate*	• Derived from human plasma • Factor VIII facilitates the activation of factor X causing the formation of thrombin and fibrin • Von Willebrand factor promotes platelet aggregation and adhesion to damaged vascular endothelium • Factor VIII potency differs by product
von Willebrand factor, recombinant *Vonvendi*	• Purified recombinant von Willebrand factor (rVWF) expressed in Chinese Hamster Ovary (CHO) cells • Acts to promote hemostasis by mediating platelet adhesion to damaged vascular sub-endothelial matrix (e.g. collagen) and

	platelet aggregation, and as a carrier protein for factor VIII, protecting it from rapid proteolysis
Antihemophilic factor porcine, recombinant *Obizur*	• Derived from baby hamster kidney cell line which secrete recombinant porcine factor VIII in cell culture medium • Replaces the inhibited factor VIII needed for effective hemostasis and normalizes the aPTT over the effective dosing period. • Factor VIII activity, not aPTT, should not be used as a measure of efficacy during treatment
Antihemophilic factor (recombinant), single chain *Afstyla*	• Uses a covalent bond to form a single polypeptide-chain (one structural entity) to improve the stability of factor VIII and provide longer-lasting factor VIII activity
Antihemophilic factor Fc fusion protein, recombinant (rFVIIIFc) *Eloctate*	• Antihemophilic factor (Factor VIII) is covalently linked to the Fc domain of human immunoglobulin G1 • Binding of Fc domain delays degradation to increase circulating half-life of factor VIII
Antihemophilic factor-recombinant, fc-vwf-xten fusion protein-ehtl Altuviiio	
Antihemophilic factor (recombinant), glycopegylated-exei *Esperoct*	
Antihemophilic factor pegylated, recombinant *Adynovate*	• Pegylated form of recombinant antihemophilic factor (Factor VIII) • Exhibits an extended terminal half-life through pegylation of the parent molecule, which reduces binding to the physiological factor VIII clearance receptor (LRP1)
Antihemophilic factor (recombinant) pegylated-aucl *Jivi*	• Site-specifically PEGylated recombinant antihemophilic factor that temporarily replaces the missing coagulation Factor VIII • The site-specific PEGylation in the A3 domain reduces binding to the physiological Factor VIII clearance receptors resulting in an extended half-life and increased AUC
Factor IX	• BeneFIX and RIXUBIS are produced in a Chinese hamster ovary cell line

Human: *AlphaNine SD, Mononine* Recombinant: *BeneFIX, RIXUBIS, Ixinity*	• Mononine is purified with a murine monoclonal antibody • Combines with factor VIII to activate factor X (factor X converts prothrombin to thrombin; thrombin converts fibrinogen to fibrin clot)
Factor IX complex *Bebulin, Profilnine SD*	• Derived from human plasma • Contains varying concentrations of factors II, VII, and X (in addition to factor IX)
Factor IX albumin fusion protein, recombinant *Idelvion*	• Recombinant factor IX molecule is genetically fused to recombinant albumin • Fusing to albumin prolongs the half-life of factor IX
Factor IX Fc fusion protein, recombinant *Alprolix*	• Human coagulation factor IX is covalently linked to the Fc domain of human immunoglobulin G1 • Binding of Fc domain delays degradation to increase circulating half-life of factor IX
Factor IX GlycoPEGylated, recombinant *Rebinyn*	• Recombinant factor IX molecule is conjugated to a polyethylene glycol molecule • Conjugating to polyethylene glycol prolongs the half-life of factor IX
Coagulation Factor X, human *Coagadex*	• Derived from human plasma • Factor X is an inactive zymogen, which can be activated by Factor IXa (via the intrinsic pathway) or by Factor VIIa (via the extrinsic pathway)
Factor XIII Human: *Corifact* Recombinant: *Tretten*	• Circulates in the blood and is found in platelets, macrophages, and monocytes • Promotes cross-linking of fibrin during the coagulation process, and protects the newly formed clot from fibrinolysis

POSITION STATEMENT:

Initiation and continuation of a clotting factor or coagulant blood product **meets the definition of medical necessity** when all of the following criteria are met:

1. Member has seen a board-certified hematologist or hematologist-oncologist in the past 12 months – documentation from medical record must be provided, including **ALL** of the following:
    a. Complete hematologic and musculoskeletal assessment performed by the physician
    b. Factor replacement protocol (including dosing for both acute and prophylactic management) has been developed or evaluated by a board-certified hematologist or

hematologist-oncologist (or a physician extender practicing under their supervision) within the past 12 months

c.

2. Requested product is prescribed by a board-certified hematologist or hematologist-oncologist (or a physician extender practicing under the supervision of a hematologist or hematologist-oncologist)
3. Member maintains a treatment log documenting any bleeds and required treatment for 12 consecutive months
    a. Long-acting or extended half-life factor VIII and IX products – a copy of the treatment log with at least 12 months of tracking bleeds must be submitted (6 months of data will be allowed if initiating therapy)
    b. All other clotting factors and coagulant blood products – a copy of the treatment log with at least 12 months of tracking bleeds must be submitted for continuation
4. Member meets product-specific criteria outlined in Table 2.

TABLE 2

Criteria for use of clotting factors and coagulant blood products[1,2]

Product	Required Criteria (ALL must be met)	Indication	Maximum Dose[2]	Maximum Dispensed Quantity[2]
Anti-inhibitor Coagulant Complex *Feiba*	1. Member is diagnosed with one of the following: a. Hemophilia A with high-titer factor VIII inhibitors (≥ 5 Bethesda units [BU]) – recent (within the past 90 days) laboratory documentation must be provided b. Hemophilia B with high-titer factor IX inhibitors (≥ 5 Bethesda units [BU]) – recent (within the past 90 days) laboratory documentation must be provided c. Acquired inhibitors (≥ 5 Bethesda units [BU]) to factors VIII, XI, and XII – recent (within the past 90	Treatment of acute bleeding episode	200 units/kg/day	5 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	100 units/kg x 1 dose	1 dose/procedure
		Routine prophylaxis of bleeding	85 units/kg every other day	15 doses/30 days

	days) laboratory documentation must be provided 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year			
Factor VIIa, recombinant *NovoSeven, NovoSeven RT*	1. Member is diagnosed with one of the following: a. Hemophilia A with high-titer factor VIII inhibitors (≥ 5 Bethesda units [BU]) – recent (within the past 90 days) laboratory documentation must be provided b. Hemophilia B with high-titer factor IX inhibitors (≥ 5 Bethesda units [BU]) – recent (within the past 90 days) laboratory documentation must be provided 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of acute bleeding episode	120 mcg/kg/dose in adults or 150 mcg/kg/dose in children	5 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	120 mcg/kg/dose in adults or 150 mcg/kg/dose in children	1 dose/procedure
	1. Member is diagnosed with acquired hemophilia 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of acute bleeding episode	90 mcg/kg/dose	5 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	90 mcg/kg/dose	1 dose/procedure
	1. Member is diagnosed with a congenital factor VII deficiency	Treatment of acute bleeding episode	30 mcg/kg/dose	5 doses

	2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year			
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	30 mcg/kg/dose	1 dose/procedure
	1. Member is diagnosed with Glanzmann's thrombasthenia 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of acute bleeding episode	90 mcg/kg/dose	5 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	90 mcg/kg/dose	1 dose/procedure
Factor VIIa, recombinant *SevenFact*	1. Member is diagnosed with one of the following: a. Hemophilia A with high-titer factor VIII inhibitors (≥ 5 Bethesda units [BU]) – recent (within the past 90 days) laboratory documentation must be provided b. Hemophilia B with high-titer factor IX inhibitors (≥ 5 Bethesda units [BU]) – recent (within the past 90 days) laboratory documentation must be provided 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of acute bleeding episode	225 mcg/kg x 1 dose, followed by 75 mcg/kg as needed Total daily doses not to exceed 900 mcg/kg.	5 doses (1 dose of 225 mcg/kg, 4 doses of 75 mcg/kg)

Factor VIII Human: *Hemofil M, Monoclate-P* Recombinant*:* *Advate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha*	1. Member is diagnosed with hemophilia A 2. Member meets **ONE** of the following: a. Indication for use is treatment of acute bleeding episode b. Indication for use is prophylaxis of post-operative bleeding c. Indication for use is routine prophylaxis of bleeding **AND** one of the following is met: i. Endogenous (baseline, not treated) factor VIII is less than or equal to 1 IU/dL (1%) – laboratory documentation must be provided (If this is the first request in a member who previously received gene therapy, laboratory documentation must be within the most recent 90 days) ii. Endogenous (baseline, not treated) factor VIII is less than or equal to 40 IU/dL (40%) **AND** either of the following – laboratory documentation must be provided (If this is the first request in a member who previously received gene therapy,	Treatment of acute bleeding episode	50 IU/kg/dose (100 IU/kg/dose if inhibitor titers are less than 10 Bethesda units/mL)	5 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	50 IU/kg/dose	1 dose/procedure
		Routine prophylaxis of bleeding	50 IU/kg/dose three times per week or every other day	15 doses/30 days
		Immune tolerance induction therapy **AND** all of the following are met: 1. Inhibitor titers are less than 10 Bethesda units/mL – recent (within the past 90 days) laboratory documentation must be provided	200 IU/kg/day	Refer to member specific protocol

	laboratory documentation must be within the most recent 90 days): 1. Indication for use is treatment of acute bleeding episode 2. Indication for use is prophylaxis of bleeding and member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) d. Indication for use is immune tolerance induction therapy 3. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	2. Inhibitor titers will be measured every six months		
Factor VIII/VWF complex	1. Member is diagnosed with von Willebrand disease 2. Member meets ONE of the following:	Treatment of acute bleeding episode (Humate P)	80 IU/kg/dose (Humate P)	5 doses (Humate P)

Alphanate, Humate P, Koate-DVI, Octanate	a. Use of desmopressin is known or suspected to be ineffective or contraindicated b. Member was previously approved for requested product by another health plan – documentation of a recent (within 90 days prior to authorization request) health plan-paid claim for the requested product must be provided 3. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	60 IU/kg/dose (Alphanate, Humate P); 75 IU/kg/dose if age < 18 years (Alphanate)	1 dose/procedure
Factor VIII/VWF complex *Wilate*	1. Member is diagnosed with von Willebrand disease **AND** one the following: 2. Member meets ONE of the following: a. Use of desmopressin is known or suspected to be ineffective or contraindicated b. Member was previously approved for requested product by another health plan – documentation of a recent (within 90 days prior to authorization request) health plan-paid claim for the requested product must be provided 3. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of acute bleeding episode, including spontaneous bleeding or trauma induced bleeding	60 IU/kg/dose	5 doses
		Perioperative management of bleeding[3] – documentation of planned procedure must be provided	60 IU/kg/dose	1 dose/procedure
		Routine prophylaxis of bleeding	40 IU/kg two to three times per week	12 doses/week
von Willebrand factor, recombinant *Vonvendi*	1. Member is diagnosed with von Willebrand disease **AND** one the following:	Treatment of acute bleeding episode, including spontaneous bleeding or	80 IU/kg/dose	5 doses

	2. Member meets ONE of the following: a. Use of desmopressin is known or suspected to be ineffective or contraindicated b. Member was previously approved for requested product by another health plan – documentation of a recent (within 90 days prior to authorization request) health plan-paid claim for the requested product must be provided 3. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	trauma induced bleeding		
Antihemophilic factor porcine, recombinant *Obizur*	1. Member is diagnosed with acquired hemophilia A 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of acute bleeding episode, including spontaneous bleeding or trauma induced bleeding	200 IU/kg/dose	5 doses
Long-acting or extended half-life factor VIII products: Antihemophilic factor (recombinant), single chain *(Afstyla)* Antihemophilic factor pegylated,	<u>Initiation of therapy</u>: 1. Member is diagnosed with hemophilia A 2. Member does not have inhibitors to factor VIII 3. Member meets **ONE** of the following: a. Endogenous (baseline, not treated) factor VIII is less than or equal to 1 IU/dL (1%) – laboratory documentation must be provided (If this is the first request in a member who previously received gene therapy, laboratory documentation must be	Treatment of acute bleeding episode	50 IU/kg/dose	5 doses Altuviiio: 2 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	50 IU/kg/dose Eloctate only: 60 IU/kg/dose	1 dose/procedure
		Routine prophylaxis of bleeding	Afstyla: 50 IU/kg/dose	Afstyla: 12 doses/30 days

recombinant *(Adynovate)* Antihemophilic factor (recombinant), glycopegylated -exei *(Esperoct)* Antihemophilic factor (recombinant) pegylated-aucl *(Jivi)* Antihemophilic factor Fc fusion protein, recombinant (rFVIIIFc) *(Eloctate)* Antihemophilic factor-recombinant, fc-vwf-xten fusion protein-ehtl *(Altuviiio)*	within the most recent 90 days) b. Endogenous (baseline, not treated) factor VIII is less than or equal to 40 IU/dL (40%) **AND** member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) –laboratory documentation must be provided (If this is the first request in a member who previously received gene therapy, laboratory documentation must be within the most recent 90 days) 4. Required if requested product is being used for routine prophylaxis of bleeding (NOT treatment of acute bleeding or prophylaxis of post-operative bleeding) – documentation from the medical record must be provided: a. The member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor VIII products when used as part of a factor replacement protocol for prophylactic management of bleeding: i. Human (plasma-derived) Factor		three times per week Adynovate, Esperoct: 50 IU/kg/dose two times per week Jivi: 60 IU/kg/dose two times per week OR 45 to 60 IU/kg/dose every 5 days Eloctate: 65 IU/kg/dose every three to five days Altuviiio: 50 IU/kg/dose weekly	Adynovate, Esperoct: 14 doses/30 days Jivi: 9 doses/30 days Eloctate: 10 doses/30 days Altuviiio: 4 doses/30 days

	VIII: Hemofil M, Monoclate-P ii. Recombinant Factor VIII: Advate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha 5. Indication-specific dose and quantity are not exceeded[2] Approval duration: 6 months <u>Continuation of therapy</u>: 1. Member was previously approved by Florida Blue or meets Florida Blue's initiation criteria 2. Member demonstrates a beneficial response according to indication for use – bleed log must be provided: a. Treatment of acute bleeding episode: Bleeding episode controlled with 2 or fewer injections b. Routine prophylaxis of bleeding: 75% reduction in ABR 3. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year			
Factor IX, human	1. Member is diagnosed with hemophilia B	Treatment of acute bleeding episode	120 IU/kg/dose	5 doses

AlphaNine SD, Mononine	2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	100 IU/kg/dose	1 dose/procedure
		Routine prophylaxis of bleeding	100 IU/kg/dose two or three times per week	12 doses/30 days
Factor IX, recombinant *BeneFIX, Ixinity, RIXUBIS*	1. Member is diagnosed with hemophilia B 2. Member meets **ONE** of the following: a. Indication for use is treatment of acute bleeding episode b. Indication for use is prophylaxis of post-operative bleeding c. Indication for use is routine prophylaxis of bleeding AND one of the following is met i. Endogenous (baseline, not treated) factor IX is less than or equal to 1 IU/dL (1%) –laboratory documentation must be provided (If this is the first request in a member who previously received gene therapy, laboratory documentation must be within the most recent 90 days)	Treatment of acute bleeding episode	140 IU/kg/dose	5 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	140 IU/kg/dose	1 dose/procedure
		Routine prophylaxis of bleeding	BeneFIX, Ixfinity: 100 IU/kg/dose two or three times per week RIXUBIS: 80 IU/kg/dose two times per week	BeneFIX, Ixfinity: 12 doses/30 days RIXUBIS: 8 doses/30 days

	ii. Endogenous (baseline, not treated) factor IX is less than or equal to 40 IU/dL (40%) **AND** either of the following – laboratory documentation must be provided (If this is the first request in a member who previously received gene therapy, laboratory documentation must be within the most recent 90 days): 1. Indication for use is treatment of acute bleeding episode 2. Indication for use is prophylaxis of bleeding and member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows,			

	shoulders) 3. Indication-specific dose and quantity are not exceeded Approval duration: 1 year			
Factor IX complex *Bebulin, Profilnine SD*	1. Member is diagnosed with hemophilia B, factor II deficiency, or factor X deficiency 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of acute bleeding episode	Bebulin: 120 IU/kg/dose Profilnine SD: 100 IU/kg/dose	5 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned procedure must be provided	Bebulin: 120 IU/kg/dose Profilnine SD: 100 IU/kg/dose	1 dose/procedure
		Routine prophylaxis of bleeding	Bebulin: 120 IU/kg/dose Profilnine SD: 100 IU/kg/dose	8 doses/30 days
Long-acting or extended half-life factor IX products: Factor IX albumin fusion protein, recombinant *(Idelvion)*	<u>Initiation of therapy</u>: 1. Member is diagnosed with hemophilia B 2. Member does not have inhibitors to factor IX 3. Member meets ONE of the following: a. Endogenous (baseline, not treated) factor IX is less than or equal to 1 IU/dL (1%) –laboratory documentation must be	Treatment of acute bleeding episode	Alprolix, Idelvion: 100 IU/kg/dose Rebinyn: 80 IU/kg/dose	Alprolix, Idelvion, Rebinyn: 2 doses
		Prophylaxis of post-operative bleeding[3] – documentation of planned	Alprolix, Idelvion: 100 IU/kg/dose	Alprolix, Idelvion, Rebinyn: 1

Factor IX Fc fusion protein, recombinant *(Alprolix)* Factor IX GlycoPEGylated, recombinant *(Rebinyn)*	provided (If this is the first request in a member who previously received gene therapy, laboratory documentation must be within the most recent 90 days) b. Endogenous (baseline, not treated) factor IX is less than or equal to 40 IU/dL (40%) AND member has documented history of 2 or more bleeds into large joints (i.e., ankles, knees, hips, elbows, shoulders) –laboratory documentation must be provided (If this is the first request in a member who previously received gene therapy, laboratory documentation must be within the most recent 90 days) 4. Required if requested product is being used for routine prophylaxis of bleeding (NOT treatment of acute bleeding or prophylaxis of post-operative bleeding) – documentation from the medical record must be provided: a. The member has had clinically evident bleeding (defined as: 1 or more episodes of spontaneous bleeding into a joint or into the central nervous system; or 4 or more episodes of soft tissue bleeding in an 8 week period) during a two month trial of at least one of the following factor VIII products when used as part of a factor replacement protocol for	procedure must be provided	Rebinyn: 80 IU/kg/dose	dose/procedure
		Routine prophylaxis of bleeding	Idelvion: 1. Age 12 years and older: 40 IU/kg one time per week or 75 IU/kg every 14 days 2. Age less than 12 years: 55 IU/kg every 7 days Alprolix: 50 IU/kg/dose one time per week or 100 IU/kg/dose every 10 days Rebinyn: 40 IU/kg once weekly	4 doses/28 days

	prophylactic management of bleeding: i. Human (plasma-derived) Factor IX (human): AlphaNine SD, Mononine ii. Factor IX, recombinant: BeneFIX, Ixinity, RIXUBIS 5. Indication-specific dose and quantity are not exceeded[2] Approval duration: 6 months <u>Continuation of therapy</u>: 1. Member was previously approved by Florida Blue or meets Florida Blue's initiation criteria 2. Member demonstrates a beneficial response according to indication for use: a. Treatment of acute bleeding episode: Bleeding episode controlled with 2 or fewer injections b. Routine prophylaxis of bleeding: 75% reduction in ABR 3. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year			
Fibrinogen concentrate *Fibryga, RiaSTAP*	1. Member is diagnosed with a congenital fibrinogen deficiency (e.g., afibrinogenemia, hypofibrinogenemia) that has been confirmed by blood coagulation testing	Treatment of acute bleeding episode	70 mg/kg/dose unless member's baseline fibrinogen	

	2. Use is **NOT** for treatment of dysfibrinogenemia 3. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year		level is known	
Coagulation Factor X, human *Coagadex*	1. Member is diagnosed with hereditary factor X deficiency 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Treatment of bleeding	25 IU/kg/dose one time every 24 hours	
		Perioperative management of bleeding AND member has mild hereditary factor X deficiency	50 IU/kg/dose	
Factor XIII, human *Corifact*	1. Member is diagnosed with congenital factor XIII deficiency – laboratory documentation of endogenous (baseline, not treated) factor XIII level must be provided (for initiation or if not previously approved by FB) 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Prophylaxis of bleeding	45 IU/kg/dose every 28 days	
Factor XIII, recombinant *Tretten*	1. Member is diagnosed with congenital factor XIII deficiency – laboratory documentation of endogenous (baseline, not treated) factor XIII level must be provided (for initiation or if not previously approved by FB) 2. Indication-specific dose and quantity are not exceeded[2] Approval duration: 1 year	Prophylaxis of bleeding	35 IU/kg/dose every 28 days	

1. Due to variations in potency and limited vial sizes, doses may be equal to or less than 110% of the doses listed above.
2. Exceptions to the listed quantity/dose will require PK studies or other medical documentation supporting clinical rationale.

3. Includes dental bleeding prophylaxis (e.g., tooth extraction)

All products listed in Table 2 are considered **experimental or investigational** for all other indications as there is insufficient clinical evidence to support use.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USE.

Dosage and administration vary considerably with each product and is based on patient weight. A brief overview of selected products is provided in Table 3; however, it is strongly recommended that the prescriber refer to product-specific labeling for complete dosing and administration instructions.

Table 3

Dosage and administration of select clotting factor and coagulant blood products	
Product	**Dosing/Administration**
Anti-inhibitor Coagulant Complex *Feiba*	**General dosing recommendation:** 50 to 100 units/kg IV (maximum total daily dose: 200 units/kg) **Joint hemorrhage:** 50 to 100 units/kg IV every 12 hours; continue until clinical improvement achieved (e.g., pain relief, reduced swelling, joint mobilization) **Mucous membrane bleeding:** 50 to 100 units/kg IV every 6 hours; carefully monitor patient and perform repeated measurements hemoglobin/hematocrit **Soft tissue hemorrhage (e.g., retroperitoneal bleeding):** 100 units/kg IV every 12 hours **Other severe hemorrhage (e.g., CNS bleed):**

	100 units/kg every 6 to 12 hours; do not exceed maximum daily dose of 200 units/kg unless bleeding severity warrants use
Fibrinogen concentrate *Fibryga, RiaSTAP*	**Baseline fibrinogen concentration NOT known:** 70 mg/kg IV (rate not to exceed 5 mL/min) **Baseline fibrinogen concentration known:** Calculate dose using known and target plasma fibrinogen level as: Dose (mg/kg) = [Target plasma fibrinogen (mg/dL) – Measured plasma fibrinogen (mg/dL)] / 1.7 mg/dL **Pediatric (age less than 16 years) :** A shorter half-life and faster clearance were observed in pediatric subjects (n=4)
Factor VIIa, recombinant *NovoSeven, NovoSeven RT*	**Administer by slow IV injection over 2 to 5 minutes within 3 hours of reconstitution** **Acute bleeding episodes in hemophilia A or B with inhibitors:** 90 mcg/kg every 2 hours until hemostasis achieved, then every 3 to 6 hours to maintain hemostatic plug **Bleeding prophylaxis during surgical interventions in hemophilia A or B with inhibitors:** 90 mcg/kg immediately before the intervention, then every 2 hours for the duration of the surgery • Minor surgery: Continue dosing every 2 hours for the first 48 hours after surgery, then every 2 to 6 hours until healing has occurred • Major surgery: Continue dosing every 2 hours for the first 5 days after surgery, then every four hours until healing has occurred **Congenital factor VII deficiency:**

	15-30 mcg/kg every 4 to 6 hours until hemostasis is achieved **Acquired hemophilia:** 70 to 90 mcg/kg every 2 to 3 hours until hemostasis is achieved
Factor VIIa, recombinant *SevenFact*	Acute bleeding episodes in hemophilia A or B with inhibitors: 225 mcg/kg x 1 dose, then 75 mcg/kg every 2 hours until hemostasis achieved
Antihemophilic factor (recombinant) pegylated-aucl *Jivi*	**General Dosing Information:** Expected recovery: one unit per kilogram body weight will increase the Factor VIII level by 2 international units per deciliter (IU/dL) Required dose (IU) = body weight (kg) x desired Factor VIII rise (% of normal or IU/dL) x reciprocal of expected recovery (or observed recovery, if available) Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg) **On-demand Treatment and Control of Bleeding Episodes** Minor event: 10 to 20 units/kg IV every 24 to 48 hours Moderate event: 15 to 30 units/kg IV every 24 to 48 hours Major event: 30 to 50 units/kg IV every 8 to 24 hours **Perioperative Management of Bleeding** Minor surgery: 15 to 30 units/kg repeat every 24 days for up to 1 day post-surgery Major surgery: 40 to 50 units/kg every 12 to 24 hours until adequate wound healing **Routine prophylaxis** 30–40 units/kg twice weekly

	Adjust dose 45-60 units/kg every 5 days based on bleeding episodes
Factor XIII Human: *Corifact*	**Initial dose:** 40 IU/kg IV (rate not to exceed 4 mL/min) every 28 days to maintain 5 to 20% trough level of factor XIII activity **Dosing adjustments**: Adjust dose ± 5 IU/kg given the most recent trough factor XIII activity. Recommended dose adjustments based on the Berichrom activity assay are given as an example below: • One trough level less than 5%: Increase dose by 5 IU/kg • Trough level 5 to 20%: No change • Two trough levels of greater than 20%: Decrease dose by 5 IU/kg • One trough level greater than 25%: Decrease dose by 5 IU/kg **Perioperative management of surgical bleeding** Individualize the dose based on the factor XIII activity level, type of surgery, and clinical response. • Time since last dose is less than 7 days: Additional dose may not be needed • Time since last dose is 7 to 21 days: Partial or full dose may be needed • Time since last dose is greater than 21 days: Full dose may be given

PRECAUTIONS:

The possibility of contamination with hepatitis and other viral or bacterial infections exists for all products derived from or purified with human blood components. The manufacturing processes are designed to reduce the risk of transmitting viral infection; however, none of the processes are completely effective. There is also the possibility that unknown infectious agents may be present. It is recommended that all members with hemophilia receive vaccination against hepatitis A and B at birth or at diagnosis of hemophilia.

Specific precautions and warnings are highlighted in Table 4.

Table 4

Precautions and warnings of clotting factor and coagulant blood products

Product	Precautions/Warnings
Anti-inhibitor Coagulant Complex *Feiba*	Use is contraindicated in individuals with acute thrombosis, embolism, or significant signs of disseminated intravascular coagulation (DIC) **(Boxed Warning)**
Fibrinogen concentrate *Fibryga, RiaSTAP*	Allergic-anaphylactic reactions and thromboembolic episodes have been reported
Factor VIIa *NovoSeven, NovoSeven RT*	Arterial and venous thrombotic and thromboembolic events are associated with use **(Boxed Warning)**
Factor VIII Human: *Hemofil M, Monoclate-P* Recombinant: *Advate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Recombinate, ReFacto, Xyntha*	Use with all factor VIII products has been associated with development of inhibitors. Monoclonal antibody-purified and recombinant antihemophilic factor products contain varying amounts of animal protein and should be used with caution in patients with bovine protein hypersensitivity, hamster protein hypersensitivity, and murine protein hypersensitivity.
Factor VIII/VWF complex *Alphanate, Humate P, Koate-DVI, Octanate, Wilate*	Contraindicated in individuals with known anaphylactic or severe systemic reaction to human plasma-derived products. Use has been associated with development of factor VIII or VWF inhibitors.
von Willebrand factor, recombinant *Vonvendi*	Use has been associated with development of factor VIII or VWF inhibitors.
Antihemophilic factor porcine, recombinant *Obizur*	Contraindicated in individuals with known anaphylactic or severe systemic reaction to hamster protein.
Antihemophilic factor (recombinant), single chain *Afstyla*	Hypersensitivity reactions, including anaphylaxis, are possible. Development of Factor VIII neutralizing antibodies (inhibitors) can occur. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's Factor VIII activity level
Antihemophilic Fc fusion protein, recombinant (rFVIIIFc) *Eloctate*	Allergic-anaphylactic reactions have been reported
Antihemophilic factor pegylated, recombinant *Adynovate*	Allergic-anaphylactic reactions have been reported
Antihemophilic factor (recombinant), glycopegylated-exei *Esperoct*	Allergic-anaphylactic reactions have been reported. Development of Factor VIII neutralizing antibodies can occur.

Antihemophilic factor (recombinant) pegylated-aucl *Jivi*	Contraindicated in patients who have a history of hypersensitivity reactions to the active substance, polyethylene glycol (PEG), mouse or hamster proteins, or other constituents of the product. Development of Factor VIII neutralizing antibodies can occur.
Factor IX Human: *AlphaNine SD, Mononine* Recombinant: *BeneFIX, RIXUBIS, Ixinity*	BeneFIX and RIXUBIS are contraindicated in individuals with a known history of hamster protein hypersensitivity. Mononine should not be used in those with murine protein hypersensitivity. Use of all factor IX products have been associated with development of factor IX inhibitors.
Factor IX albumin fusion protein, recombinant *Idelvion*	Contraindicated in individuals with known anaphylactic or severe systemic reaction to hamster protein.
Factor IX Fc fusion protein, recombinant *Alprolix*	Allergic-anaphylactic reactions and thromboembolic episodes have been reported
Factor IX complex *Bebulin, Profilnine SD*	Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections
Factor IX GlycoPEGylated, recombinant *Rebinyn*	Allergic-anaphylactic reactions and thromboembolic episodes have been reported
Coagulation Factor X, human *Coagadex*	Hypersensitivity reactions, including anaphylaxis, are possible. Development of neutralizing antibodies (inhibitors) may occur.
Factor XIII Human: *Corifact*	Contraindicated in individuals with known anaphylactic or severe systemic reaction to human plasma-derived products. Use has been associated with development of factor XIII inhibitors.

BILLING/CODING INFORMATION:

The following codes may be used to report clotting factor and coagulant blood products:

HCPCS Coding:

J7175	Injection, factor x, (human), 1 IU [for Coagadex only]
J7177	Injection, human fibrinogen concentrate, Fibryga, 1 mg
J7178	Injection, human fibrinogen concentrate, not otherwise specified, 1 mg
J7179	Injection, von willebrand factor (recombinant), Vonvendi, 1 IU vwf:rco
J7180	Injection, factor XIII (antihemophilic factor, human), 1 IU
J7181	Injection, factor XIII A-subunit, (recombinant), per IU
J7182	Injection, factor viii, (antihemophilic factor, recombinant), Novoeight, per IU
J7183	Injection, von Willebrand factor complex (human), Wilate®, 1 IU VWF:RCO
J7185	Injection, factor VII (antihemophilic factor, recombinant), Xyntha, per IU

J7186	Injection, antihemophilic factor VIII/Von Willebrand factor complex (human), per factor VIII IU
J7187	Injection, von Willebrand Factor complex, Humate-P, per IU vWF-RCO
J7188	Injection, factor viii (antihemophilic factor, recombinant), Obizur, per IU
J7189	Factor VIIa (antihemophilic factor, recombinant), (Novoseven RT), 1 microgram
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	Injection, factor IX (antihemophilic factor, recombinant), per IU, not otherwise specified
J7198	Anti-inhibitor, per IU
J7199	Hemophilia clotting factor, not otherwise classified
J7200	Injection, factor IX, (antihemophilic factor, recombinant), Rixubis, per IU
J7201	Injection, factor IX, Fc fusion protein (recombinant), Alprolix, 1 IU
J7202	Injection, factor ix, albumin fusion protein, (recombinant), Idelvion, 1 IU
J7203	Injection factor ix, (antihemophilic factor, recombinant), glycopegylated, (Rebinyn), 1 IU
J7204	Injection, factor viii, antihemophilic factor (recombinant), (esperoct), glycopegylated-exei, per iu
J7205	Injection, factor viii fc fusion protein (recombinant), per IU
J7207	Injection, factor viii, (antihemophilic factor, recombinant), pegylated, 1 IU
J7208	Injection, factor viii, (antihemophilic factor, recombinant), pegylated-aucl, (jivi), 1 IU
J7209	Injection, factor viii, (antihemophilic factor, recombinant), Nuwiq, 1 IU
J7210	Injection, factor viii, (antihemophilic factor, recombinant), Afstyla, 1 IU
J7211	Injection, factor viii, (antihemophilic factor, recombinant), Kovaltry, 1 IU
J7212	Factor viia (antihemophilic factor, recombinant)-jncw (Sevenfact), 1 microgram
J7213	Injection, coagulation factor ix (recombinant), Ixinity, 1 IU
J7214	Injection, factor viii/von willebrand factor complex, recombinant (Altuviiio), per factor viii IU

ICD-10 Diagnosis Codes That Support Medical Necessity:

D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency
D68.0	Von Willebrand's disease
D68.1	Hereditary factor XI deficiency
D68.2	Hereditary deficiency of other clotting factors

D68.31	Hemorrhagic disorder due to intrinsic circulating anticoagulants
D68.32	Hemorrhagic disorder due to extrinsic circulating anticoagulants
D68.4	Acquired coagulation factor deficiency
D69.1	Qualitative platelet defects

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage Products: The following National Coverage Determination (NCD) was reviewed on the last guideline revised date: Anti-Inhibitor Coagulant Complex (AICC) (110.3) located at cms.gov. The following Local Coverage Determination (LCD) located at www.fcso.com was reviewed on the last guideline revised date: Hemophilia Clotting Factors (L33684).

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Afibrinogenemia: lack of fibrinogen (coagulation factor I) in the blood.

AHF: Nonspecific antihemophilic factor is a preparation of factor VIII administered intravenously for the prevention or treatment of hemorrhage in patients with hemophilia A and the treatment of von Willebrand disease, hypofibrinogenemia and factor VIII deficiency.

AICC: Anti-Inhibitor Coagulant Complex is a concentrated fraction from pooled human plasma, which includes various coagulation factors. It is administered intravenously as an antihemorrhagic in hemophilic patients with inhibitors to factor XIII.

Congenital Afibrinogenemia: a rare autosomal recessive hemorrhagic coagulation disorder, characterized by complete incoagulability of the blood; hemorrhagic manifestations vary from mild to serious.

Dysfibrinogenemia: the presence in the blood of abnormal fibrinogen; both autosomal dominant and recessive forms are known.

Hemophilia B (Christmas Disease): a common type of hemophilia, an X-linked condition caused by deficiency of factor IX.

Hypofibrinogenemia: abnormally low levels of fibrinogen in the blood; called also fibrinogenopenia.

RELATED GUIDELINES:

None applicable.

OTHER:

Guidelines to first and second choice treatment:

Patient's Inhibitor	Clinical Situation		
Titer	Minor bleeding	Major bleeding	Surgery (emergency)
Less than 5 BU	AHF	AHF	AHF
5 to 10 BU	AHF	AHF	AHF
	AICC	AICC	AICC
More than 10 BU	AICC	AICC	AICC

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COMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/14/25.

GUIDELINE UPDATE INFORMATION:

03/15/01	New Medical Coverage Guideline.
04/15/03	Reviewed with no changes.
01/01/06	Annual HCPCS coding update: added new code J7190 and revised codes J7191 – J7193.
06/15/06	Reviewed with changing of HCPCS codes that were listed as CPT-4 codes and deleted one HCPCS code that was for Factor IX. Also added brand names.
03/15/07	MCG changed to No Longer Reviewed (NLR).
07/15/07	Reviewed guideline: maintain current coverage and limitations. Reformatted guideline, updated internet links and references.
01/01/08	Annual HCPCS coding update: added HCPCS code J7187.
09/15/08	Review and revision to guideline; consisting of renaming guideline, added factor VIIa and factor IX, updated “Description” section, updated position statement, updated coding and updated references and links.
01/01/09	Annual HCPCS coding update: deleted 90765 and 90766; added J7186, 96365 and 96366.
07/01/09	HCPCS 3rd quarter coding update: added Q2023.
10/15/09	Review and revision to guideline; consisting of Incorporating Anti-Inhibitor Coagulant Complex into MCG, adding fibrinogen and updating references.
01/01/10	Annual HCPCS coding update: added J1680 and J7185, revised J7192 descriptor, and deleted Q2023.
05/15/10	Review and revision to guideline; consisting of updating drug lists, ICD-9 coding and HCPCS codes.
01/01/11	Revision to guideline; consisting of updating coding.
05/15/11	Review and revision to guideline; consisting of adding new agent, updating dosing and references.
07/01/11	Revision to guideline; consisting of updating coding.
10/01/11	Revision to guideline; consisting of updating coding.
01/01/12	Revision to guideline; consisting of updating coding.
05/15/12	Review and revision to guideline; consisting of updating of descriptions, reformatting updating coding and references
01/01/13	Annual HCPCS Update; added HCPCS code J7178 and removed J1680.
05/15/13	Review and revision to guideline; consisting of updating references, reformatting position statement.
12/15/13	Revision to guideline; consisting of description, position statement, precautions/warnings, and references.

05/15/14	Review and revision to guideline; consisting of position statement, dosage/administration, references, program exceptions.
09/15/14	Revision to guideline; consisting of description, position statement, dosage/administration, precautions, coding, references
01/01/15	Revision to guideline; consisting of coding, position statement, and annual HCPCS coding update.
03/15/15	Revision to guideline; consisting of position statement, coding.
05/15/15	Revision to guideline; consisting of position statement, precautions, references.
09/15/15	Revision to guideline; consisting of position statement, precautions, references.
10/01/15	Revision consisting of update to Program Exceptions section.
01/01/16	Annual HCPCS coding update: added codes J7188 and J7205 and delete code Q9975.
02/15/16	Revision to guideline; consisting of updating position statement.
03/15/16	Revision to guideline; consisting of updating position statement with new FDA approved agents, change MCG name from Antihemophilic Agents to Clotting Factor and Coagulant Blood Products.
04/01/16	Revision to guideline consisting of adding codes C9137 and C9138.
05/15/16	Review and revision to guideline consisting of updating position statement with newly approved agents, updating coding, references.
06/15/16	Revision to guideline consisting of updating coding.
07/15/16	Revision to guideline consisting of updating position statement.
09/15/16	Revision to guideline consisting of updating position statement to include Afstyla.
10/01/16	Revision: New HCPCS code C9139 added.
01/01/17	Revision: added HCPCS codes J7175, J7179, J7202, J7207, and J7209.
05/15/17	Review and revision to guidelines; consisting of updating references.
01/01/18	Updated HCPCS coding.
01/15/18	Revision to guideline; consisting of updating position statement to include Rebinyn.
03/15/18	Revision to guideline; consisting of updating position statement to include Hemlibra.
04/01/18	Addition of HCPCS code C9468.
05/15/18	Review and revision to guidelines; consisting of updating coding and references.
07/01/18	Addition of HCPCS code Q9995 for Hemlibra.
12/15/18	Revision to guideline; consisting of updating position statement to include Jivi (Antihemophilic Factor (Recombinant) PEGylated-aucl).
01/01/19	Revision to guideline; consisting of updating position statement.
03/15/19	Revision to guideline; consisting of updating position statement.
04/15/19	Revision to guideline; consisting of updating HCPCS coding.
05/15/19	Review and revision to guidelines; consisting of updating position statement and references.
06/15/19	Revision to guideline; consisting of updating position statement to include Esperoct (Turoctocog alfa pegol).
07/01/19	Revision: added HCPCS code J7208.
01/01/20	Update to position statement.
07/15/20	Revision to position statement.
11/15/20	Revision to position statement.

01/01/21	Revision: Added HCPCS code J7212 and revised description on code J7189.
03/15/23	Revision to position statement to include Rebinyn prophylaxis dosing.
07/01/23	Review and revision to guideline. Addition of Altuviiio. Addition of HCPCS code J7213.
10/01/23	Revision: Added HCPCS code J7214.
04/01/24	Revision: Removed Hemlibra from Medical Coverage Guideline.
06/15/25	Revision to position statement.
12/15/25	Revision to position statement.