Coagulation Factor VIIa Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date 05-26-2025 **Date of Origin**

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
NovoSeven RT® (coagulation Factor VIIa, recombinant) Lyophilized powder for solution, for intravenous use	• Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets • Treatment of bleeding episodes and perioperative management in adults with acquired hemophilia		1
Sevenfact® (coagulation Factor VIIa [recombinant] -jncw) Lyophilized powder for solution, for intravenous use	• Treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with Hemophilia A or B with inhibitors Limitation of Use: Sevenfact is not indicated for treatment of congenital factor VII deficiency		2

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Congenital hemophilia A and congenital hemophilia B	Congenital hemophilia A and congenital hemophilia B are genetic disorders caused by missing or defective Factor VIII (FVIII) (for hemophilia A) and Factor IX (FIX) (for hemophilia B), a clotting protein. Although it is passed down from parents to children, about 1/3 of cases found have no previous family history.(3-4) People with hemophilia A and hemophilia B bleed longer than other people. Bleeds can occur internally, into joints and muscles, or externally, from minor cuts, dental procedures, or injuries. How often a person bleeds and the severity of those bleeds depends on how much FVIII or FIX a person produces naturally.(3-4) Inhibitor development is the most severe complication of treatment for patients with inherited hemophilia A or B. Choice of product for treatment depends on multiple factors, including type of inhibitor (low- or high- responding), current titer of inhibitor, location of the bleed, previous response to a product, availability of clinical trial data

	supporting use of the products and concomitant medications (e.g., emicizumab). For high-titer inhibitors immune tolerance induction (ITI) is the best option for inhibitor eradication.(5) If left unchecked a persistent inhibitor will present a severe burden on patients and families as the ongoing physical, emotional, and in many cases financial toll continue to intensify. Healthcare providers will often attempt to proactively stamp out an inhibitor through ITI. ITI is an approach to inhibitor eradication where the body's immune system begins to tolerate a therapy after daily doses of factor are administered over time. The majority of people who undergo ITI therapy will see an improvement within 12 months, but more difficult cases can take two years or longer. There is a general consensus that failure of ITI is the inability to achieve successful tolerance within 2-3 years of initiation of an ITI regimen.(12) ITI can take several months to several years to be effective. The Hemophilia Federation of America recommends that if success has not occurred within 33 months of beginning ITI and there is a lack of a 20% decrease in the inhibitor titer over a 6 month period that it is considered a failure.(13) In the cases of high-responding inhibitors treatment is based on several components including the type of hemophilia and the nature of the bleed. During a life or limb-threatening bleeding episode physicians can remove antibodies from the body using plasmapheresis. This is only a temporary solution however as within a few days the body will produce large amounts of new antibodies. For the person with high responding inhibitors there are therapies that can effectively treat bleeds by circumventing the need to replace FVIII. These agents are commonly referred to as bypassing agents (BPAs) and include activated prothrombin complex concentrate (aPCC) and recombinant activated Factor VII concentrates (rFVIIa).(6) To date, the evidence for the benefits of secondary prophylaxis as compared to on-demand treatment of hemophilic patients with inhibitors is limited. In a randomized, double blind, prospective clinical trial secondary prophylaxis in patients with congenital hemophilia A and B with inhibitors was evaluated. The primary efficacy endpoint was number of bleeds per month during the prophylaxis period as compared to the pre-prophylaxis period. A bleed was defined as rebleeding if it occurred at the same site within 6 hours of treatment and episodes beginning 6 hours after treatment or occurring in another site were defined as a new episode. Secondary efficacy endpoints included the number of bleeds per month occurring in the post-prophylaxis period as compared to those observed in the observation and prophylaxis period, at specific bleeding sites (target joint, joint, muscle, soft-tissue bleeds), and cause of bleed (traumatic, spontaneous and other) over the entire trial period.(7) The observed benefits of rFVIIa prophylaxis in hemophilic patients with inhibitors were consistent with reports of secondary prophylactic treatment in patients without inhibitors. Bleeding frequency was reduced by 45-59% during prophylaxis with doses of 90 and 270 mcg/kg respectively (p less than 0.0001). Although all types of bleeds were similarly reduced, the effect was most pronounced for spontaneous joint bleeds.(7) Treatments for patients with inhibitors continue to be investigated. Sequential or concomitant therapy with rFVIIa and aPCC might be helpful in difficult to treat patients for whom monotherapy with either agent is ineffective. Clinical data is limited, and more substantial, well-controlled studies evaluating this approach are needed. Combined use of the two agents should only be carried out in the inpatient setting that has experience of this treatment, along with careful monitoring.(14) Another form of combination therapy involves the administration of FVIII with either rFVIIa or aPCC for prophylaxis. An invitro study using plasma from patients with high-titer inhibitors demonstrated that the addition of FVIII enhanced the hemostatic effect of both bypassing agents. FVIII combined with aPCC had a synergistic effect on thrombin formation, whereas FVIII combined with rFVIIa had an additive effect.(14)

Acquired hemophilia A	Under certain conditions individuals who were not born with hemophilia may develop antibodies or inhibitors that cause destruction of FVIII resulting in clinical bleeding due to very low levels of this clotting factor. Such inhibitors may be seen in patients with cancer, systemic lupus erythematosus, and other autoimmune disorders. Often no associated condition can be identified.(5) Although about 1/3 of patients do not require therapy to control bleeds, bleeding severity varies and more than 1/3 of patients had multiple bleeding episodes. Subcutaneous bleeding (ecchymoses) is the most common manifestation of acquired hemophilia followed by hematoma, melena, hematuria, and retroperitoneal. Intracranial hemorrhage is rare but can be fatal. In contrast to congenital hemophilia A, joint bleeding is infrequent.(8)
Congenital Factor VII deficiency:	Factor VII (FVII), or proconvertin, deficiency was first recognized in 1951. Considered the most common of rare bleeding disorders its incidence is estimated at 1 per 300,000-500,000. It is inherited in an autosomal recessive fashion, and it affects men and women equally. FVII is a protein that, when bound to tissue factor, initiates the clotting cascade which leads to the formation of a blood clot.(9) Symptoms are usually linked to the level of FVII in the blood but not always. For instance, some people with low FVII levels may have mild symptoms. Babies are often diagnosed with FVII deficiency within the first 6 months of life, after sustaining a bleed in the central nervous system, such as an intracranial hemorrhage, or gastrointestinal tract. People with severe FVII deficiency experience joint and muscle bleeds, easy bruising, and bleeds after surgery. Bleeds can also occur in the skin, mouth, nose and genitourinary tract. Women often experience severe menorrhagia.(9) The main treatment for FVII deficiency is recombinant Factor VIIa (rFVIIa). Prothrombin complex concentrates (PCCs) can also be used, but the amount of Factor VII they contain can vary considerably. Fresh frozen plasma (FFP) is also an option.(9) Because of the very short half-life of FVII, prophylaxis in FVII deficiency is considered a difficult endeavor. The clinical efficacy and safety of prophylactic regimens, and indications for their use, were evaluated in FVII deficient patient in the Seven Treatment Evaluation Registry (STER). Information was recorded in the STER database from 34 patients with FVII deficiency receiving prophylaxis in 13 hemophilia centers (11 countries).(10) The reasons for initiating prophylaxis and the treatment regimens used varied among the patients analyzed. Overall prophylaxis yielded “excellent” results in 68% of the courses.(10)
Glanzmann's thrombasthenia	People with Glanzmann’s thrombasthenia (GT) have platelets that lack a protein (glycoprotein IIb/IIIa) that helps them stick together to form a clot. Laboratory tests are needed to diagnose GT. The symptoms of GT include bruising, petechiae, nosebleeds, and heavy menstrual bleeding. GT affects approximately 1 in a million people.(11)
Efficacy	NovoSeven RT is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process may also occur on the surface of activated platelets.(1) The active ingredient in Sevenfact is a recombinant analog of human Factor VIIa, a vitamin K-dependent coagulation factor. In the presence of both calcium and phospholipids, Factor VIIa in a complex with tissue factor (TF) activates Factor X to Factor Xa, directly bypassing the reactions that require Factor VIII or Factor IX. Activation of Factor X to Factor Xa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin, which then converts fibrinogen to fibrin to form a hemostatic plug, thereby achieving clot formation at the site of hemorrhage.(2)

Safety	• **NovoSeven RT** has no known contraindications but does contain a boxed warning of:(1)
	  ○ Serious arterial and venous thrombotic events following administration of NovoSeven RT
	  ○ Discuss the risks and explain the sign and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven RT
	  ○ Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis
	• **Sevenfact** is contraindicated in:(2)
	  ○ Known allergy to rabbits or rabbit proteins
	  ○ Severe hypersensitivity reaction to Sevenfact or any of its components
	• **Sevenfact** contains a boxed warning of:(2)
	  ○ Serious arterial and venous thrombotic events may occur following administration of Sevenfact
	  ○ Discuss the risk and explain the sign and symptoms of thrombotic and thromboembolic events to patients who will receive Sevenfact
	  ○ Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis

REFERENCES

Number	Reference
1	NovoSeven RT Prescribing Information. Novo Nordisk Inc. July 2020.
2	Sevenfact Prescribing Information. LFB S.A. November 2022.
3	National Hemophilia Foundation. Bleeding disorders A-Z/Types/Hemophilia A. Accessed at https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a.
4	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Hemophilia B. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b.
5	Medical and Scientific Advisory Council (MASAC) MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Document #280. August 2023.
6	National Hemophilia Foundation Bleeding Disorders A-Z Overview Inhibitors Treatment for Inhibitors. Treatment for Inhibitors | National Hemophilia Foundation.
7	Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. J Thromb Haemost 2007; 5: 1904-13.
8	National Organization for Rare Disorders (NORD). Rare Disease Database. Acquired Hemophilia. Accessed at: https://rarediseases.org/rare-diseases/acquired-hemophilia/.
9	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Other Factor Deficiencies/Factor VII. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/other-factor-deficiencies/factor-vii.
10	Napolitano M, Glanslly-Blalzot M, Dolce A, et al. Prophylaxis in congenital factor VII deficiency: indications, efficacy and safety. Results from the Seven Treatment Evaluation Registry (STER). Haematologica 2013 Apr; 98(4):538-44.
11	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Inherited Platelet Disorders. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/inherited-platelet-disorders.

Number	Reference
12	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.
13	Dimichele DM, Hoots WK, Pipe SW, et al. International workshop on immune tolerance induction: consensus recommendations. Haemophilia (2007), 13 (Suppl. 1), 1-22.
14	Ljung R, Auerswald G, Benson G, et al. Inhibitors in haemophilia A and B: Management of bleeds, inhibitor eradication and strategies for difficult-to-treat patients. Eur J Haematol. 2019;102:111-122.
15	Reference no longer used

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J7189	Novoseven rt	coagulation factor viia (recomb) for inj	1 MG ; 2 MG ; 5 MG ; 8 MG	M ; N ; O ; Y	N		
J7212	Sevenfact	coagulation factor viia (recom)-jncw for inj	1 MG ; 2 MG ; 5 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Novoseven rt	coagulation factor viia (recomb) for inj	1 MG ; 2 MG ; 5 MG ; 8 MG	Commercial ; HIM ; ResultsRx
Sevenfact	coagulation factor viia (recom)-jncw for inj	1 MG ; 2 MG ; 5 MG	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Novoseven rt	coagulation factor viia (recomb) for inj	8 MG	Commercial ; HIM ; ResultsRx
Novoseven rt	coagulation factor viia (recomb) for inj	1 MG	Commercial ; HIM ; ResultsRx
Novoseven rt	coagulation factor viia (recomb) for inj	2 MG	Commercial ; HIM ; ResultsRx
Novoseven rt	coagulation factor viia (recomb) for inj	5 MG	Commercial ; HIM ; ResultsRx
Sevenfact	coagulation factor viia (recom)-jncw for inj	1 MG	Commercial ; HIM ; ResultsRx
Sevenfact	coagulation factor viia (recom)-jncw for inj	5 MG	Commercial ; HIM ; ResultsRx
Sevenfact	coagulation factor viia (recom)-jncw for inj	2 MG	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
NovoSeven RT	**NovoSeven RT** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. ONE of the following: A. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of hemophilia A AND BOTH of the following: 1. The patient has inhibitors to Factor VIII **AND** 2. The requested agent is being used for ONE of the following: A. On-demand use for bleeds AND ONE of the following: 1. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** 2. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** B. Prophylaxis AND ALL of the following: 1. ONE of the following: A. The patient has tried and had an inadequate response to Immune Tolerance Induction (ITI) [Immune Tolerance Therapy (ITT)] **OR** B. The patient has an inhibitor level greater than or equal to 200 BU (lab records required) **OR** C. The patient is not a candidate for ITI **AND** 2. The patient will NOT be using the requested agent in combination with Hemlibra **AND** 3. The patient will NOT be using the requested agent in combination with Feiba [activated prothrombin complex (aPCC)] used for prophylaxis (on-demand use of aPCC is acceptable) **OR** C. Peri-operative management of bleeding **OR** D. As a component of Immune tolerance induction (ITI)/Immune tolerance therapy (ITT) AND ONE of the following: 1. The patient has NOT had more than 33 months of ITT/ITI therapy **OR** 2. There is support for the continued use of ITT/ITI therapy (i.e., the patient has had a greater than or equal to 20% decrease in inhibitor level over the last 6 months and needs further treatment to eradicate inhibitors) (medical records required) **OR** B. The patient has a diagnosis of hemophilia B AND BOTH of the following: 1. The patient has inhibitors to Factor IX **AND** 2. The requested agent is being used for ONE of the following: A. On-demand use for bleeds AND ONE of the following: 1. The prescriber communicated with the patient (via any means) regarding the

Module	Clinical Criteria for Approval
	frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** 2. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** B. Prophylaxis AND BOTH of the following: 1. ONE of the following: A. The patient has tried and had an inadequate response to Immune Tolerance Induction (ITI) [Immune Tolerance Therapy (ITT)] **OR** B. The patient has an inhibitor level greater than or equal to 200 BU (lab records required) **OR** C. The patient is not a candidate for ITI **AND** 2. The patient will NOT be using the requested agent in combination with Feiba [activated prothrombin complex (aPCC)] used for prophylaxis (on-demand use of aPCC is acceptable) **OR** C. Peri-operative management of bleeding **OR** D. As a component of Immune tolerance induction (ITI)/Immune tolerance therapy (ITT) AND ONE of the following: 1. The patient has NOT had more than 33 months of ITT/ITI therapy **OR** 2. There is support for the continued use of ITT/ITI therapy (i.e., the patient has had a greater than or equal to 20% decrease in inhibitor level over the last 6 months and needs further treatment to eradicate inhibitors) (medical records required) **OR** C. The patient has a diagnosis of congenital Factor VII deficiency AND the requested agent will be used for ONE of the following: 1. On-demand use for bleeds AND ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** 2. Prophylaxis **OR** 3. Perioperative use **OR** D. The patient has a diagnosis of Glanzmann's thrombasthenia AND BOTH of the following: 1. The patient is refractory to platelet transfusions **AND** 2. The requested agent will be used for ONE of the following: A. On-demand use for bleeds AND ONE of the following: 1. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient

Module	Clinical Criteria for Approval
	does not have greater than 5 on-demand doses on hand **OR** 2. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** B. Perioperative use **OR** E. The patient has a diagnosis of acquired hemophilia AND the requested agent will be used for ONE of the following: 1. On-demand use for bleeds AND ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** 2. Perioperative use **OR** F. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** B. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient will NOT be using the requested agent in combination with another Factor VIIa agent **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. ONE of the following: A. The requested quantity (dose) does NOT exceed the program quantity limit defined by BOTH of the following: 1. The requested dose is within the FDA labeled dosing **AND** 2. The requested quantity (number of doses) is appropriate based on intended use (e.g., on-demand, prophylaxis, perioperative) **OR** B. There is support for exceeding the appropriate quantity limit based on the FDA labeled dosing and/or intended use (medical records required) **Length of Approval:** • Peri-operative dosing: 1 time per request • On**-**demand: up to 3 months • Prophylaxis: up to 12 months • ITT/ITI: up to 6 months, or up to a total of 33 months of ITT/ITI therapy, or requested duration - whichever is shortest • All other indications: 3 months **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence
Sevenfact	**Sevenfact** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of hemophilia A AND BOTH of the following: 1. The patient has inhibitors to Factor VIII **AND** 2. The requested agent is being used for on-demand use for bleeds **OR**

Module	Clinical Criteria for Approval
	B. The patient has a diagnosis of hemophilia B AND BOTH of the following: 1. The patient has inhibitors to Factor IX **AND** 2. The requested agent is being used for on-demand use for bleeds **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another Factor VIIa agent **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **AND** 7. ONE of the following: A. The requested quantity (dose) does NOT exceed the program quantity limit defined by BOTH of the following: 1. The requested dose is within the FDA labeled dosing **AND** 2. The requested quantity (number of doses) is appropriate based on intended use (e.g., on-demand) **OR** B. There is support for exceeding the appropriate quantity limit based on the FDA labeled dose and/or intended use (medical records required) **Length of Approval:** up to 3 months