POLICY: Hemophilia – Eptacog Products

- NovoSeven® RT (Coagulation Factor VIIa [recombinant] for intravenous use – Novo Nordisk)

APPROVAL DATE: 10/02/2019

OVERVIEW

NovoSeven RT is indicated for treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets.[1] It is also indicated for treatment of bleeding episodes and perioperative management in adults with acquired hemophilia. It is produced by recombinant technology in baby hamster kidney cells. Exogenous viruses are removed through a chromatographic purification process. No human serum or other proteins are used in the production or formulation of NovoSeven RT. The half-life of NovoSeven RT is short (approximately 2 to 3 hours in patients with hemophilia A, hemophilia B, or congenital Factor VII deficiency), therefore frequent dosing is often required.

Disease Overview

Hemophilia A is an X-linked bleeding disorder caused by a deficiency in coagulation Factor VIII.[2] The birth prevalence of hemophilia A in the US is approximately 1:6,500 live male births. **Hemophilia B**, caused by deficiency in Coagulation Factor IX, is clinically indistinguishable from hemophilia A and is also inherited in an X-linked manner.[3] The birth prevalence is approximately 1:30,000 live male births. Bleeding episodes are treated with plasma-derived or recombinant Factor VIII or Factor IX concentrates. These agents are also given prophylactically for individuals with severe disease.

Approximately 30% of patients with severe hemophilia A and 1 to 3% of patients with severe hemophilia B develop alloimmune inhibitors (antibodies) to Factor VIII or Factor IX concentrate.[2,3] In **acquired hemophilia A**, individuals who were not born with hemophilia develop inhibitors to endogenous Factor VIII.[4] Certain conditions, including cancer, lupus erythematosus, and other autoimmune disorders, may predispose patients to development of acquired hemophilia A. In both acquired and congenital hemophilia, presence of inhibitors at high titers makes the factor replacement ineffective, and alternative "bypassing" agents are needed to promote hemostasis. Examples of commercially available bypassing agents include NovoSeven RT, as well as FEIBA® (anti-inhibitor coagulant complex for intravenous use).[5] Hemlibra® (emiczumab-kxwh for subcutaneous use) is a monoclonal antibody that mimics the action of Factor VIII and therefore is only indicated in hemophilia A.

Glanzmann's thrombasthenia (GT) is a genetic disorder of the glycoprotein IIb/IIIa complex on the platelet surface, which results in faulty platelet aggregation and diminished clot retraction.[6] The exact incidence is unknown but is estimated at approximately 1:1,000,000 individuals. Most individuals are diagnosed before 5 years of age. Prophylactic therapy is not needed, but treatment is necessary for surgical procedures and to control acute bleeding episodes. Platelet transfusion is considered standard therapy if local measures are inadequate to control bleeding. NovoSeven RT has been successfully used in patients who are refractory to platelet transfusions or to avoid the need for transfusion. **Congenital Factor VII deficiency** is a rare autosomal recessive disorder affecting an estimated 1:300,000 to 1:500,000 individuals.[7,8] NovoSeven RT is the standard treatment for this condition.

Of note, off-label use of NovoSeven RT in the general population has been suggested in a variety of acute bleeding scenarios (e.g., trauma, intracranial hemorrhage). A 2012 Cochrane Review concluded that the

effectiveness of recombinant activated Factor VIIa as a general hemostatic drug in non-hemophiliac patients remains unproven and that use outside its licensed indications should be limited to clinical trials.[9] Various reviews and clinical practice guidelines concur that the evidence is insufficient to support use of NovoSeven RT as a hemostatic agent outside of its labeled uses.[10-12]

Guidelines

The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia and other bleeding disorders.[2] NovoSeven RT is supported as a treatment option for inherited hemophilia A or B with inhibitors, acquired hemophilia A, and Factor VII deficiency (Glanzmann's thrombasthenia is not addressed in the guidelines). MASAC recommendations (2013) also state that NovoSeven RT and FEIBA have demonstrated efficacy and safety for prophylactic use for patients with inhibitors in hemophilia A and hemophilia B.[13]

Dosing Information

Dosing of clotting factor concentrates is highly individualized. MASAC provides recommendations regarding doses of clotting factor concentrate in the home (2016).[14] The number of required doses varies greatly and is dependent on the severity of the disorder and the prescribed regimen. Per MASAC guidance, patients on prophylaxis should also have a minimum of one major dose and two minor doses on hand for breakthrough episodes in addition to the prophylactic doses used monthly. The guidance also notes that an adequate supply of clotting factor concentrate is needed to accommodate weekends and holidays. Therefore, maximum doses in this policy allow for prophylactic dosing plus three days of acute episodes or perioperative management per 28 days. Doses exceeding this quantity will be reviewed on a case-by-case basis by a clinician.

Dosing considerations for individual indications are as follows:

- **Congenital Factor VII Deficiency:** In the routine prophylactic setting, recombinant Factor VIIa dosing of up to 30 mcg/kg three times weekly has been described in literature.[8] Per prescribing information, dosing for bleeding episodes and perioperative management ranges up to 30 mcg/kg up to every 4 hours (180 mcg/kg daily dose).[1]
- **Glanzmann's Thrombasthenia:** Prophylactic dosing is not routine. Per the prescribing information, dosing up to 90 mcg/kg every 2 hours may be used for acute episodes or perioperative management (1,080 mcg/kg daily dose).[1]
- **Hemophilia A, Acquired:** Data are limited describing prophylactic use of recombinant Factor VIIa in acquired hemophilia; dosing is generally similar to what is used for congenital hemophilia A and B with inhibitors. Per the prescribing information, dosing up to 90 mcg/kg every 2 hours may be used for acute episodes or perioperative management (1,080 mcg/kg daily dose).[1]
- **Hemophilia A with Inhibitors** and **Hemophilia B with Inhibitors:** For congenital hemophilia A and B with inhibitors, MASAC recommendations note that doses of up to 270 mcg/kg per day have been found to be effective.[13] Per the prescribing information, dosing up to 50 mcg/kg per hour by continuous infusion may be used in the perioperative setting (1,200 mcg/kg daily dose).[1]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of NovoSeven RT. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

Because of the specialized skills required for evaluation and diagnosis of patients treated with NovoSeven RT as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of NovoSeven RT is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Congenital Factor VII Deficiency.** Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 900 mcg/kg intravenously per 28 days.

2. **Glanzmann's Thrombasthenia.** Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hematologist.

   Dosing. Approve up to 3,240 mcg/kg intravenously per 28 days.

3. **Hemophilia A, Acquired.** Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 10,800 mcg/kg intravenously per 28 days.

4. **Hemophilia A with Inhibitors.** Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 11,160 mcg/kg intravenously per 28 days.

5. **Hemophilia B with Inhibitors.** Approve for 1 year if NovoSeven RT is prescribed by or in consultation with a hemophilia specialist.

   Dosing. Approve up to 11,160 mcg/kg intravenously per 28 days.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

NovoSeven RT has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Bleeding Associated with Liver Disease.** Randomized trials have failed to show benefit of NovoSeven RT in controlling upper gastrointestinal bleeding and variceal bleeding in patients with

advanced liver disease.[15,16] American Association for the Study of Liver Disease guidelines for portal hypertensive bleeding in cirrhosis (2016) state that recombinant Factor VIIa should not be used to correct coagulopathy in this scenario.[17]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Approval Date
New policy	--	10/02/2019