PDL DRUG REVIEW

Proprietary Name: Sevenfact®
Common Name: coagulation factor VIIa (recombinant)-jncw
PDL Category: Antihemophilic Agents

Comparable Products	Preferred Drug List Status
NovoSeven	Preferred

Summary

Pharmacology/Usage: Sevenfact® contains coagulation Factor VIIa (recombinant)-jncw as the active ingredient. It is produced by recombinant DNA technology using genetically engineered rabbits into which the DNA coding sequence for human Factor VII has been introduced. Human Factor VII is expressed in the rabbit mammary gland and secreted into the milk. During purification and processing, Factor VII is enzymatically converted to activated Factor VII. The manufacturing process of Sevenfact® includes specific steps to reduce impurities. Sevenfact® may contain trace amounts of rabbit proteins.

Thus, 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, thus achieving clot formation at the site of hemorrhage. This process may also occur in the absence of TF on the surface of activated platelets.

Indication: For the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors. A limitation of use is that Sevenfact® is not indicated for the treatment of patients with congenital Factor VII deficiency.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate and well-controlled studies using Sevenfact® in pregnant women to determine whether there is a drug-associated risk. It is not known whether Sevenfact® can cause fetal harm when administered to a pregnant woman or can affect fertility. The safety and efficacy of use in the pediatric population under the age of 12 years have not been established.

Dosage Form: Lyophilized powder for reconstitution in a colorless solution for injection, supplied in single-dose vial sizes containing 1mg or 5mg of coagulation factor VIIa (recombinant)-jncw. The diluent for reconstitution is supplied in single-dose prefilled glass syringes containing 1.1ml or 5.2ml sterile Water for injection. After reconstitution with the appropriate volume of Water for Injection diluent, each ml contains 1mg per ml of coagulation factor VIIa (recombinant)-jncw (1000mcg/ml).

Recommended Dosage: For IV use only. The dose and duration of treatment depend on the location and severity of the bleeding, need for urgent homeostasis, frequency of administration, and known patient responsiveness to Factor VIIa-containing bypassing agents during prior bleeding events. Sevenfact® treatment should be started as soon as a bleeding event occurs.

The dose, frequency, and duration of Sevenfact® should be based on the patient's clinical response and hemostasis evaluation. Maximum tolerated doses have not been determined, and cumulative daily doses greater than 900mcg/kg, which may be associated with greater risk of thromboembolic complications, have not been studied.

Dose adjustment may be required if the patient has received other procoagulant therapies prior to treatment with Sevenfact®.

For mild and moderate bleeding, the recommended dosing regimen is 75mcg/kg repeated every 3 hours until hemostasis is achieved. Continue therapy to support healing and prevent recurrent hemorrhage after hemostasis to maintain the hemostatic plug. The site and severity of bleeding should determine therapy duration. Or, administer an initial dose of 225mcg/kg; if hemostasis is not achieved within 9 hours, additional 75mcg/kg doses may be administered every 3 hours as needed to achieve hemostasis. Consider alternative treatments if successful control of bleeding does not occur within 24 hours of the first administration of Sevenfact®. Consider the following factors when choosing the initial dose of Sevenfact®:

- The severity and site of bleeding and need for urgent hemostasis
- Frequency of administration
- Known patient responsiveness to Factor VIIa-containing bypassing agents during prior bleeding events.

For severe bleeding, the recommended dosing regimen is 225mcg/kg initially, followed if necessary 6 hours later with 75mcg/kg every 2 hours until hemostasis is achieved. With subsequent dosing, after achieving hemostasis, base the decision for dosing on clinical assessment and the type of bleeding. Consider the risk of thrombosis with subsequent dosing after achieving hemostatic efficacy. Continue therapy to support healing and prevent recurrent hemorrhage. The site and severity of bleeding and the use of other procoagulant therapies should determine therapy duration.

The safety and efficacy of Sevenfact® in patients >65 years of age have not been assessed in clinical trials. The presence of age-related comorbidities and the attendant risks associated with thrombotic and thromboembolic events should be considered when administering Sevenfact® to patients older than 50 years of age.

Drug Interactions: Clinical experience with pharmacologic use of Factor VIIa-containing products indicates an elevated risk of serious thrombotic events when used simultaneously with activated prothrombin complex concentrates.

Box Warning: Sevenfact® has a box warning regarding the increased risk of thrombosis. Serious arterial and venous thrombotic events may occur following administration of Sevenfact®. Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive Sevenfact®. In addition, monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis.

Common Adverse Drug Reactions: *There was no placebo data to compare with in the prescribing information.* There were 27 subjects in study 1; there were a total of 7 adverse reactions that were observed in two subjects (7.4%). These adverse reactions included infusion site discomfort (4), infusion site hematoma (2), and body temperature increased (1). There were 15 subjects in study 2; there were a total of three subjects (20%) who experienced 4 adverse reactions. These reported adverse events included dizziness (2), headache (1), and infusion related reaction (1).

There is limited information about the safety of Sevenfact® in patients with a history of arterial or venous thromboembolic disease, as such patients were excluded from Sevenfact® trials. Serious arterial and venous thrombotic reactions can occur with Sevenfact®. Certain patients may have increased risk of thromboembolic events with use of Sevenfact®, such as those with a history of atherosclerotic disease, coronary artery disease, cerebrovascular disease, crush injury, septicemia, thromboembolism, or history of congenital or acquired hemophilia receiving concomitant treatment with other hemostatic agents. Monitor patients receiving Sevenfact® for the development of signs and symptoms of activation of the coagulation system or thrombosis.

In the studies performed, no patients tested positive for neutralizing antibodies. Nevertheless, neutralizing antibodies may occur with the use of Sevenfact®. If treatment with Sevenfact® does not result in adequate hemostasis, then suspect development of neutralizing antibody as the possible cause and perform testing as clinically indicated. Neutralizing antibodies to other Factor VIIa-containing products have been observed in congenital Factor VII-deficient patients. Sevenfact® has not been studied in this patient population.

Contraindications: In:

- Known allergy to rabbits or rabbit proteins. Exposure to Sevenfact® in these patients can result in severe hypersensitivity reaction
- Patients with severe hypersensitivity reaction to Sevenfact® or any of its components. Exposure to Sevenfact® in these patients can result in severe hypersensitivity reaction.

Manufacturer: Laboratoire Francais du Fractionnement; Distributed by HEMA Biologics.

Analysis: The safety and efficacy of Sevenfact® for the treatment of bleeding episodes were assessed in Study 1, a multicenter, randomized, open-label crossover of two initial dose regimens that included subjects with hemophilia A or B with inhibitors (N=27) who were treated for 468 bleeding events, of which 465 were mild or moderate and 3 were severe bleeding events. Of the 27 subjects, 5 were 12 to <18 years of age and they experienced 79 bleeding events. All subjects were male and primarily Caucasian (93%), with a mean age of 31 years (range 12-54) and median of 10 bleeding episodes in the 6 months prior to study entry. Overall, target joint(s)/bleeding site(s) were reported in 63% of subjects at study entry. All doses of Sevenfact® were given at home or in the clinic.

Of the 468 bleeding events that were treated, 82% were spontaneous and the remaining (18%) were traumatic bleeding episodes; 465 were mild or moderate bleeding events and 3 were severe. Most of the bleeding events (98%) were treated at home, with 88% treated within one hour of recognition of bleeding. The primary endpoint was successful treatment of mild or moderate bleeding episode at 12 hours after initial Sevenfact® dose administration. Success was defined by a combination of the following: subject's response of 'good' or 'excellent' using a 4-point hemostatic efficacy scale, no further treatment with Sevenfact® beyond the 12-hour time point, no other hemostatic treatment needed for the bleeding episode, no administration of blood products, and no increase in pain beyond 12 hours. See table below for the hemostatic efficacy scale, which was adapted from the prescribing information.

Patient and/or Healthcare Provider Evaluation	Therapeutic Response	Description
None	Lack of hemostatic efficacy	No noticeable effect of the treatment on bleeding or worsening of subject's condition. Continuation with study drug was needed
Moderate	Lack of hemostatic efficacy	Some effect of treatment on bleeding was noticed but bleeding continued & required continued treatment with study drug
Good	Hemostatic efficacy	Symptoms of the bleeding largely reduced by treatment but not completely disappeared. Symptoms had improved enough to not require more infusions of the study drug
Excellent	Hemostatic efficacy	Full relief of pain & cessation of objective signs of bleeding. No additional infusion of study drug was required

The primary efficacy analysis compared hemostatic efficacy of each dosing regimen with a prespecified objective performance criterion (OPC) of 55%. This OPC was based on historical data for hemostatic efficacy of bypassing agents. This study was powered to detect a 15% improvement over OPC for each dosing regimen. Results can be seen in the table below, which was adapted from the prescribing information.

Of the 465 mild or moderate bleeding episodes, 17 bleeding events were not evaluable due to missing a hemostatic efficacy assessment at 12 hours. The proportion of mild or moderate bleeding events with hemostatic efficacy at 12 hours was 82% in the 75mcg/kg dose regimen group and 91% in the 225mcg/kg dose regimen group. Hemostatic efficacy was assessed in 79 bleeding events in the 5 adolescent subjects. For the 75mcg/kg dose regimen, hemostatic efficacy was 93% and for the 225mcg/kg dose regimen it was 91%.

	75mcg/kg (N=25)[1]	225mcg/kg (N=25)[1]	Overall (N=27)[1]
Number of bleeding episodes	252	213	465
Number of bleeds with hemostatic efficacy	197 (78.1%)	188 (88.2%)	385 (82.8%)
Number of failures	44 (17.4%)	19 (8.9%)	63 (13.5%)
Number of missing	11 (4.3%)	6 (2.8%)	17 (3.7%)
Proportion of bleeds with hemostatic efficacy	82%	91%	86%
p-value[2]	<0.001	<0.001	

[1] N in the column header indicates number of subjects who had at least 1 bleeding episode treated with a given dose of study drug
[2] p-value from 1-sided normal approximation test of H0: p≤0.55, where p is the true proportion of successfully treated mild or moderate bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given subject. The null hypothesis of hemostatic efficacy less than or equal to 55% was rejected.

The median and mean number of administrations per mild or moderate bleeding episode were 2.0 and 2.5 for the 75mcg/kg dose regimen and 1.0 and 1.4 for the 225mcg/kg dose regimen. The median time to attain good or excellent assessment by the patient was 6 hours for the 75mcg/kg dose regimen and 3 hours for the 225mcg/kg dose regimen.

There were 3 severe bleeding episodes, of which one was a traumatic intramuscular bleeding episode and 2 were spontaneous bleeding episodes in the right hip and kidney. Hemostasis was achieved at 12 hours in the 3 severe bleeding events. One severe bleed was treated with three 225mcg/kg doses administered every 6 hours, which was a deviation from the study protocol-specified dosing. The remaining 2 subjects were treated with 1 and 5 doses of Sevenfact®, respectively.

No subject received any alternative therapy prior to 24 hours. In addition, 97.6% of bleeding episodes treated with the 75mcg/kg dose regimen, and 99.5% of bleeding episodes treated with the 225mcg/kg dose regimen did not require treatment with alternative bypassing agents.

Place in Therapy: Sevenfact®, a recombinant analog of human Factor VIIa (coagulation factor VIIa [recombinant]-jncw) is indicated for the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors. Sevenfact® is not indicated for the treatment of patients with congenital Factor VII deficiency. In a clinical study, the proportion of mild or moderate bleeds with hemostatic efficacy at 12 hours was 82% with the 75mcg/kg dosing regimen and 91% in the 225mcg/kg dosing regimen. The median number of infusions needed to achieve bleeding control in the first 12 hours per mild or moderate bleeding episodes was 1 for the 225mcg/kg dosing regimen and 2 in the 75mcg/kg dosing regimen.

There is some evidence at this time to support that Sevenfact® is safer and more effective than conventional bypass agents, but not NovoSeven®. It is therefore recommended that Sevenfact® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Sevenfact [package insert]. Louisville, KY: HEMA Biologics; 2020.