Factor VIIa (recombinant)-jncw (SEVENFACT®)
Drug Monograph
March 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action	SEVENFACT is a recombinant analog of human Factor VIIa (rFVIIa), which in a complex with tissue factor, activates Factor X to Factor Xa and bypasses reactions requiring Factor VIII or Factor IX; also known as eptacog beta
Indication(s) under Review	Indicated for the treatment and control of bleeding episodes in adults and adolescents aged ≥ 12 years with hemophilia A or B with inhibitors
Dosage Form(s) under Review	Coagulation factor VIIa (recombinant)-jncw as a lyophilized powder in 1mg or 5mg single-use vials; once reconstituted with 1.1ml (1mg) or 5.2 ml (5mg), final concentration = 1 mg (1000 mcg)/ml

Hemophilia is a rare X-linked congenital bleeding disorder caused by a deficiency in factor VIII (hemophilia A) or factor IX (hemophilia B). Factor deficiencies are due to pathogenic variants in F8 and F9 clotting factor genes, which are usually inherited. However ~ 30% of cases result from spontaneous genetic variants [5]. Estimated prevalence of males with hemophilia worldwide is 1,125,000 with the majority undiagnosed. Hemophilia A is more common than hemophilia B, accounting for 80-85% of all cases.

Replacement with clotting factor concentrates (CFCs) for treatment and prophylaxis of bleeds, is the mainstay of therapy. An estimated 20-30% of patients with severe hemophilia A eventually develop neutralizing alloantibodies or inhibitors. The estimate is lower in severe hemophilia B at 3-5%. Inhibitors are encountered much less in mild-moderate hemophilia. They are also more common in hemophilia A than hemophilia B. When inhibitors are present, standard CFCs are no longer effective.

Bypassing agents achieve hemostasis through different mechanisms. Recombinant activated factor VIIa (rFVIIa) binds to tissue factor activating factor X to XI conversion, thus allowing the coagulation cascade to continue. Activated prothrombin complex concentrates (aPCC) are composed of non-activated factors II, IX, X and activated factor VII.

Clinical Evidence

Table 1: Efficacy results from clinical trials

Study	Design	Intervention	Endpoints	Results
PERSEPT1 Wang, et al. N=27 5 age 12-18; mAge 31 yrs; median#BE/ 6 mos = 10	Phase 3, randomized, cross-over; Males w/congenital Hemophilia A or B; Inhibitor test ≥ 5 BU (or < 5 BU if expect refractory response to factor tx per med history); ≥ 3 BE in 6 months; Purpose: Evaluate on-demand tx of mild/mod bleed events (BE)	rFVIIa-jncw (eptacog beta) 75 mcg/kg x1 or 225 mcg/kg x1 Plus 75 mcg/kg subsequent doses until response	Primary endpoint = sustained clinical response w/in 12 hrs w/o rebleed in 24 hrs Response = composite objective and pain measures Hemostatic efficacy (HE) scale (none-mod-good-excellent) Good-excellent responses required no further tx; compared with prespecified objective performance criterion (OPC) 55% [historical data for efficacy of BPAs] Pain via VAS (0-100) at baseline, hrs 12 & 24	Hemostatic efficacy 75 mcg/kg: #BE 252; HE 82% [72, 91%]; Fail 17.4%; Mean # doses Mild BE 2; Mean # doses Mod BE 2.5; TTR 6 hrs 225 mcg/kg: #BE 213; HE 91% [84, 98%]; Fail 8.9%; Mean # doses Mild BE 1; Mean # doses Mod BE 1.4; TTR 3 hrs 225 mcg/kg dosing arm: 85% of BEs were tx w/just 1 dose No detectable immunogenic or thrombotic responses noted; 44% TRAEs were non-hemophilia related
PERSEPT 2 Included patients age < 12 yrs; not included in review				
PERSEPT 3 Escobar M, et al. N=12 Males with congenital hem A or B + inhibitors	Phase 3, MC, single-arm, open-label Purpose: Evaluate efficacy of eptacog beta in elective surgical procedures	N=6; Major procedures rec'd 200 mcg/kg preop; + 75 mcg/kg doses up to 5 days; N=6; Minor procedures rec'd 75 mcg/kg preop; + 75 mcg/kg doses up to 2 days	Efficacy via 4-pt HE scale @ intraop and postop periods by surgeon/investigator Primary endpoint: Success = good or excellent assessment @ 48 hrs (based on totality of assessment)	HE Minor procedures: 100% [95% CI; 46-100%] Major procedures: 66.7% [95% CI: 22.3-95.7%]; Overall 81.8% of procedures were successful No thrombotic events or immune responses reported

Safety Summary

Boxed warnings	Thrombosis. Serious arterial and venous thrombotic events have been reported with rFVIIa
Contraindications	Known allergy to rabbits or rabbit proteins; Severe hypersensitivity reaction to rFVIIa or its components
Warnings/Precautions	Patients with other risk factors for thrombosis may be at increased risk of serious arterial or venous thrombotic events Hypersensitivity reactions, including anaphylaxis, are possible
Adverse reactions	Most common (≥ 1%): headache, dizziness, infusion-site discomfort, infusion-site hematoma, infusion-related reactions, fever

Therapeutic Alternatives

Table 3. Bypassing Agents for Patients with Hemophilia A or B and Inhibitors

Drug	Formulary status	Clinical Guidance	Other Considerations
rFVIIa-jncw **eptacog beta** SEVENFACT	TBD	N/A	Indications: treatment/control BEs in adults and adolescents ≥ 12 yrs with hemophilia A or B with inhibitors; Derived from genetically engineered rabbits; Risk of thrombosis with emicizumab unknown (non-factor agent) PADR report 2/2022-2/2023: none entered
rFVIIa **eptacog alfa** NOVOSEVEN	NF	N/A	Indications: treatment of BE and perioperative mgmt. of Hemophilia A or B with inhibitors; congenital Factor VII deficiency; Glanzmann's thrombasthenia with refractoriness to platelet transfusions with or w/o antibodies to platelets; Treatment of BE and perioperative mgmt. in adults with acquired hemophilia; Derived from baby hamster kidney cells; Does not ↑ thrombotic risk with emicizumab; FENOC trial: no efficacy difference btw eptacog alfa and aPCC FY22: 36 unique patients; PADR report: none entered
Anti-inhibitor coagulation complex (aPCC) [inactivated factors II, IX, X, VIIa] FEIBA	NF	N/A	Indications: prevention of BEs, periop mgmt., routine prophylaxis to reduce BEs in patients with hemophilia A or B with inhibitors; Derived from human plasma; ↑ thrombotic risk with emicizumab; FENOC trial: no efficacy difference btw eptacog alfa and aPCC PADR report 2/2022-2/2023: 100% approval; 1 use; 1 approval

Summary

- Eptacog beta has not been directly compared to other BPAs. Currently, the only comparative evidence among BPAs is the FENOC study, where eptacog alfa was compared to aPCC in patients with hemophilia A with inhibitors.
- aPCC is the most cost-effective treatment in patients who are not receiving emicizumab.
    - For those on emicizumab prophylaxis, either eptacog alfa or eptacog beta are reasonable options
    - Eptacog alfa is an older product with more FDA-approved indications and dosed more frequently
    - Eptacog beta is currently approved in one setting
- In the setting of congenital hemophilia A or B with inhibitors, eptacog beta may be less costly, requiring less doses per bleed event
- Eptacog alfa is expected to come off patent in 2025. A biosimilar, AryoSeven, is anticipated to be available at that time.
- Despite anticipated low use, bypassing agents should be available for use on VANF without restrictions.

References/Contact Information

1. Coagulation factor VIIa (recombinant)-jncw SEVENFACT Prescribing Information. Louisville, KY. HEMA Biiologics, LLC. November 2022

2. Wang M, et al. PERSEPT 1: a phase 3 trial of activated eptacog beta for on-demand treatment of haemophilia inhibitor-related bleeding. Haemophilia 2017; 23: 832-843.

3. Escobar M, et al. The safety of activated eptacog beta in the management of bleeding episodes and perioperative haemostasis in adult and pediatric hemophilia patients with inhibitors. Haemophilia 2021; 27: 921-931

4. Astermark J, et al. A randomized comparison of bypassing agents in hemophilia complicated by an inhibitor: the FEIBA NovoSeven Comparative (FENOC) Study. Blood 2007; 109: 546-551

5. Srivastava A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia 2020; 26 (Suppl 6): 1-158.

6. Escobar M, et al. PERSEPT 3: A phase 3 clinical trial to evaluate the hemostatic efficacy of eptacog beta (rhFVIIa) in perioperative care in subjects with hemophilia A or B with inhibitors. Haemophilia 2021; 27: 889.

Prepared Jan 2023. Contact person: Berni Heron, Pharm.D., BCOP, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)