University of Colorado Hemophilia & Thrombosis Center Pharmacy:
SPECIALTY PRODUCTS FOR TREATMENT OF FACTOR VIII OR IX INHIBITORS & ACQUIRED HEMOPHILIA

Hemophilia and Thrombosis Center
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

	FEIBA-NF ™	NOVOSEVEN-RT®	OBIZUR™	HEMLIBRA®
MANUFACTURER	SHIRE (formerly Baxalta)	NOVO NORDISK	SHIRE (formerly Baxalta)	GENENTECH (Roche Group)
US LICENSURE DATE	1986	1999	2014	2017
CLASSIFICATION	ACTIVATED PCC (Prothrombin Concentrate Complex)	"Bypassing activity" Recombinant human coagulation Factor VIIa (rFVIIa) that promotes hemostasis by activating the extrinsic pathway of the coagulation cascade.	Recombinant analogue of porcine FVIII, the B-domain has been replaced with 24 amino acid linker.	Bispecific factor IXa- and factor X-directed antibody
FDA APPROVED INDICATION	For use in hemophilia A and B patients with inhibitors for: ☑Control and prevention of bleeding episodes ☑Perioperative management ☑Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.	For use in hemophilia A or B with inhibitors, acquired hemophilia, Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets: ☑Prevention of bleeding in surgical interventions or invasive procedures Factor VII deficiency: ☑ Prevention and control of bleeding episodes ☑ Perioperative management -Safety and efficacy of NovoSeven RT has not been established outside these approved indications.	-Treatment of bleeding episodes in adults with **acquired** Hemophilia A -Safety and efficacy of OBIZUR has not been established in patients with baseline anti-porcine factor VIII inhibitor titer greater than 20 BU.	For use in hemophilia A >12 yo with inhibitors for ☑Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
CONTENTS	FEIBA contains mainly non-activated factors II, IX, and X and mainly activated factor VII. It contains approximately equal units of factor VIII inhibitor bypassing activity and prothrombin complex factors. Anti-Inhibitor Coagulant Complex.	Activated VIIa	FVIII	Humanized monoclonal modified IgG4 antibody with a bispecific antibody structure binding factor IXa and factor X.
FACTOR II	Non-activated form			
FACTOR VII	Activated form			
FACTOR IX	Non-activated form			
FACTOR X	Non-activated form			
CELL LINE FORMULATION, SOURCE MATERIAL	Pooled human plasma	Recombinant, baby hamster kidney (BHK) cell line	Recombinant porcine, baby hamster kidney (BHK) cell line	Recombinant, Chinese Hamster Ovary (CHO)

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DOSING GUIDELINES	**Control and Prevention of bleeding**: 50-100 units/kg determined by the type of bleeding episode. **Perioperative Management**: 50-100 units/kg determined by the type of surgical intervention **Routine Prophylaxis:** 85 units/kg every other day **•Do not exceed a single dose of 100 units per kg body weight and a daily dose of 200 units per kg body due to increased risk of thromboembolic events.**	**Hemophilia A or B with inhibitor:** **Bleeding episodes:** 90 mcg/kg bolus every 2 hours, adjusted based on severity of bleeding until hemostasis is achieved. Post-hemostatic dosing every 3-6 hours for severe bleeds. **Minor surgery**: 90 mcg/kg immediately before surgery and every 2 hours during surgery and for 48 hours after surgery. Then 90 mcg/kg every 2-6 hours, until healing has occurred. **Major surgery:** 90 mcg/kg immediately before surgery and every 2 hours during surgery; then 90 mcg/kg every 2 hours for the first 5 days. Continued every 4 hours, until healing has occurred. **Congenital FVII Deficiency**: Bleeding episodes: 15-30 mcg/kg every 4-6 hours until hemostasis is achieved Surgery: 15-30 mcg/kg immediately before surgery and every 4-6 hours for the duration of surgery and until hemostasis is achieved **Acquired Hemophilia-Bleeding episode or surgery:** **Bleeding Episode:** 70-90 mcg/kg every 2-3 hours until hemostasis is achieved. Surgery: 70-90 mcg/kg immediately before surgery and every 2-3 hours for the duration of surgery and until hemostasis is achieved. **Glanzmann's Thrombasthenia**: Bleeding Episode: 90 mcg/kg every 2-6 hours until hemostasis is achieved Surgery: 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure, then 90 mcg/kg every 2-6 hours to prevent post-operative bleeding	**Bleeding Episodes:** **Minor and Moderate (superficial) muscle bleed:** **Factor VIII Level Required:** 50-100 units/dL **Initial dose:** 200 iu/kg/dose titrate subsequent doses to maintain a recommended FVIII trough levels and individual response. Dose every 4 to 12 hours, frequency may be adjusted based on clinical response and measured factor VIII levels. **Major (severe intramuscular, retroperitoneal, gastrointestinal) Bleeds:** Factor VIII Levels Required: 100-200 units/dL for acute bleed. 50-100 units/dL after acute bleed is controlled, if required. **Loading dose** : 200 iu/kg/dose, titrate subsequent doses to maintain recommended FVIII trough levels and individual clinical response. Dose every 4 to 12 hours, frequency may be adjusted based on clinical response and measured FVIII levels. •Patient's half-life may vary; titrate dose and frequency based on factor VIII recovery levels and individual clinical response. •Plasma levels of factor VIII should not exceed 200% of normal or 200 units/dL.	**Prophylaxis:** 3 mg/kg subcutaneously once weekly for first 4 weeks, then 1.5 mg/kg once weekly, 3 mg/kg once every two weeks or 6 mg/kg once every four weeks.

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PROTEIN PURIFICATION	•Ion exchange chromatography •Ultrafiltration	•Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)	•Chromatography • Filtration	N/A
VIRAL INACTIVATION METHODS	•Vapor Heat; nanofiltration •DEAE-Sephadex adsorption	Chromatography	•Solvent/Detergent •Nanofiltration	N/A
MEAN HALF-LIFE	FII: ~72 Hrs	Healthy Patients (ages 20-45) :3.9-6.0 hrs Hemophilia A or B (ages 15-63): 2.89 hrs FVII deficient (ages 20-43): 2.82-3.11 hrs	Variable	27.8 ±8.1 days Due to long half-life of HEMLIBRA effects on coagulation assays may persist for up to 6 months after last dose.
INACTIVE INGREDIENTS	Trisodium citrate, NaCl	Histidine, trace amounts of mouse IgG, bovine IgG, and protein from baby hamster kidney-cells	NaCl, tris-bas, tris-HCl, tri-sodium citrate dehydrate, calcium chloride dehydrate, sucrose, polysorbate-80	L-arginine, L-histadine, poloxamer 188, L-aspartic Acid
DRUG INTERACTIONS	•Consider the possibility of thrombotic events when systemic anti-fibrinolytics such as tranexamic acid and aminocaproic acid are used. •No adequate and well-controlled studies of the combined or sequential use of FEIBA and factor VIIa or anti-fibrinolytics have been conducted. Use of anti-fibrinolytics within approximately 6 to 12 hours after the administration of FEIBA is not recommended. Cases of TMA and Thrombotic events were reported from clinical trials when an average cumulative amount of > 100 IU/kg/24 hours of activated prothrombin complex concentrate (ex. Feiba) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis.	•Avoid simultaneous use of NovoSeven and aPCCs/PCCs (activated or non-activated prothrombin complex concentrates) •Do not mix with other infusion solutions. •Do not administer NovoSeven RT with coagulation factor FXIII thrombosis may occur.		**Thrombotic Microangiopathy Associated and Thromboembolism with HEMLIBRA and APCC**. Cases of TMA and Thrombotic events were reported from clinical trials when an average cumulative amount of > 100 IU/kg/24 hours of activated prothrombin complex concentrate (ex. Feiba) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. There is the possibility for hypercoagulability with rFVIIa or FVIII with HEMLIBRA based on preclinical experiments.

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AVAILABLE ASSAYS	500 IU, 1000 IU, 2000 IU	1 mg (1000 mcg) , 2 mg (2000 mcg),5 mg (5000 mcg) 8 mg (8000 mcg)	500 IU	30 mg/1 mL in a single-dose vial 60 mg/0.4 mL in a single-dose vial 105 mg/0.7 mL in a single-dose vial 150 mg/1 mL in a single-dose vial
INFUSION RATE	2 units/kg/minute, A syringe pump may be used to control the rate of administration. Administer within 3 hours of reconstitution.	Slowly over 2-5 minutes After reconstitution, store either at room temperature or refrigerated for up to 3 hours. After reconstitution with specified volume of histidine diluent, the final solution contains 1mg per ml of rFVIIa.	1-2 mL/minute Use within 3 hours of reconstitution.	Subcutaneously injection
BOX CONTENTS	Diluent: 10 mL (500), 20 mL (1000), 50 mL (2500) Sterile Water for Injection, BAXJECT II high flow needleless transfer device.	One pre-filled histidine diluent syringe: 1.1 mL (1 mg) , 2.1 mL (2mg) , 5.2mL (5 mg) , 8.1 mL (8mg), vial adapter for needleless reconstitution.	Prefilled syringe with 1 mL Sterile Water for Injection, vial adapter with filter.	Vial of colorless to slightly yellow solution in single-dose vial
STORAGE REQUIREMENTS	▫Store at room temperature ≤ 25°C (77°F). ▫Do not freeze. ▫ Store in the original package and protect from light.	▫Store at room temperature 2 to 25°C (36 to 77°F). ▫Do not freeze. ▫Store in the original package and protect from light.	▫Refrigerate 2 to 8°C (36°F to 46°F) to expiration date. ▫Do not freeze. ▫Store in the original package and protect from light.	Refrigerate 2 to 8°C (36°F to 46°F) to expiration date. ▫Do not freeze. ▫Store in the original package and protect from light

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COMMENTS	**WARNING: THROMBOEMBOLIC EVENTS** Thromboembolic events have been reported during post-marketing surveillance, particularly following the administration of high doses and /or in patients with thrombotic risk factors. Monitor patients receiving FEIBA for signs and symptoms of thromboembolic events. **PRECAUTION**: FEIBA can cause thromboembolic events following doses above 200 units/kg/day and in patients with thrombotic risk. Monitor patients for signs and symptoms of thromboembolic events. Contains 1-6 units of factor VIII coagulant antigen (FVIII C:Ag) per mL.	**CAUTION**: The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches, and is compatible with a standard Luer-lock connector. Some needleless connectors for IV catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave®/MicroClave®, InVision-Plus CS®, InVision-Plus Junior®, Bionector®), and their use can damage the connector and affect administration. To administer product through incompatible needleless connectors, withdraw reconstituted product into a standard 10 mL sterile Luer-lock plastic syringe. **WARNING: THROMBOSIS** • Serious arterial and venous thrombotic events following administration of NovoSeven have been reported. • Discuss the risks and explain the signs 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. NOTE: To avoid product waste, dose should be calculated to nearest complete vial size		**WARNING AND PRECAUTIONS:** **Thrombotic Microangiopathy Associated and Thromboembolism with HEMLIBRA and aPCC**. Cases of TMA and Thrombotic events were reported from clinical trials when an average cumulative amount of > 100 IU/kg/24 hours of activated prothrombin complex concentrate (ex. Feiba) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis. MASAC Recommendations: Use of aPCC for breakthrough bleed treatment for patients on HEMLIBRA should be avoided if possible, and rFVIIa should be the first option used to treat. If aPCC is used, it should be limited to no more than 50 IU//kg as an initial dose and not to exceed 100 IU/kg/day. **Drug-Laboratory Test Interactions**: HEMLIBRA affects intrinsic pathway clotting-based laboratory tests, including all assays based on aPTT, Bethesda assays for FVIII inhibitor titers and activated clotting time (ACT) aPTT-based assays including clot-based FVIII activity assays with yield artificially shortened aPTT Laboratory results **unaffected** by HEMLIBRA: -Chromogenic FVIII assays will only provide an assessment of HEMLIBRA activity if the assay includes all human reagents. -Thrombin time - Bethesda assays (bovine chromogenic) - One-stage, prothrombin time based, single-factor assay -Immuno-based assays (i.e. ELISA) **Due to the long half-life of HEMLIBRA, effects on coagulation assays may persist for up to 6 months after the last dose.**

NOTE: Recombinant technology may be the ONLY product of choice for patients of Jehovah's Witnesses faith.

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