

Hemophilia Products – Coagulation Factor XIII A-subunit: Tretten® (Intravenous)

Effective date: 10/1/2019

Review date: 1/29/2020, 7/15/2021, 6/16/2022, 6/22/2023, 12/07/2023, 01/04/2024, 08/14/2024, 09/17/2025

Scope: Medicaid*, Commercial*, Medicare-

*(Medication only available on the Medical Benefit)

I. Length of Authorization

Unless otherwise specified*, the initial authorization will be provided for 3 months and may be renewed.

Note: The cumulative amount of medication the patient has on-hand will be taken into account for authorizations. Up to 5 'on-hand' doses for the treatment of acute bleeding episodes will be permitted at the time of the authorization request.

** Initial and renewal authorization periods may vary by specific covered indication*

II. Dosing Limits

– **Max Units (per dose and over time) [Medical Benefit]:**

– 4,025 billable units per 28 day supply

III. Summary of Evidence

Tretten, Coagulation Factor XIII A-Subunit (Recombinant), is indicated for routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency. Tretten replaces deficient FXIII A-subunit, binds to FXIII B-subunit to form A2B2 complex, and upon activation by thrombin and calcium, cross-links fibrin to stabilize clots and prevent bleeding. A multicenter, open-label, non-controlled trial evaluated the efficacy of monthly Tretten (35 IU/kg) in 41 subjects aged ≥6 years with congenital FXIII A-subunit deficiency over 52 weeks. The primary endpoint was the annualized rate of bleeding episodes requiring treatment with an FXIII-containing product, assessed during monthly prophylaxis therapy. Subjects had a documented history of bleeding or family history of FXIII deficiency, and severe bleeders were excluded. During 434 subject-months, five trauma-related bleeds requiring FXIII treatment occurred in four subjects, corresponding to a mean annual bleeding rate of 0.14 per subject year (calculated for 41 subjects), significantly lower than the historical on-demand rate of 1.68. In a second ongoing trial including 34 of the original and 21 new subjects (total N=55), the mean annual bleeding rate was 0.056 per subject year over 107.5 subject-years, with an age-adjusted rate of 0.022 and lower bleeding rates in adults (0.026) than in pediatric subjects (0.127), confirming sustained efficacy of Tretten prophylaxis in reducing bleeding episodes. The most common adverse reactions include headache, extremity pain, and increase in fibrin D dimer levels.

IV. Initial Approval Criteria

Hemophilia Management Program
Requirements for half-life study and inhibitor tests are a part of the hemophilia management program. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide.

A. Tretten

Coverage is provided in the following conditions:

- Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements.

Congenital Factor XIII A-subunit deficiency † Φ Diagnosis of congenital factor XIII A-subunit deficiency has been confirmed by blood coagulation testing; **AND**

- Used for routine prophylaxis of bleeding

Hemophilia Management Program
- If the request is for routine prophylaxis and the requested dose exceeds dosing limits under part II, a half-life study should be performed to determine the appropriate dose and dosing interval. - For members with a BMI ≥ 30, a half-life study should be performed to determine the appropriate dose and dosing interval. - For minimally treated patients (< 50 exposure days to factor products) previously receiving a different factor product, inhibitor testing is required at baseline, then at every comprehensive care visit (yearly for the mild and moderate patients, semi-annually for the severe patients).

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

V. Dispensing Requirements for Rendering Providers (Hemophilia Management Program)

- Prescriptions cannot be filled without an expressed need from the patient, caregiver or prescribing practitioner. Auto-filling is not allowed.
- Monthly, rendering provider must submit for authorization of dispensing quantity before delivering factor product. Information submitted must include:
 - Original prescription information, requested amount to be dispensed, vial sizes available to be ordered from the manufacturer, and patient clinical history (including patient product inventory and bleed history)
 - Factor dose should not exceed +1% of the prescribed dose and a maximum of three vials may be dispensed per dose. If unable to provide factor dosing within the required threshold, below the required threshold, the lowest possible dose able to be achieved above +1% should be dispensed. Prescribed dose should not be increased to meet assay management requirements.

- The cumulative amount of medication(s) the patient has on-hand should be taken into account when dispensing factor product. Patients should not have more than 5 extra doses on-hand for the treatment of acute bleeding episodes.
- Dispensing requirements for renderings providers are a part of the hemophilia management program. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide.

VI. Renewal Criteria

Coverage may be renewed based upon the following criteria:

- Patient continues to meet criteria identified in section IV; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: symptoms of allergic-anaphylactic reactions (anaphylaxis, dyspnea, rash, urticaria, tightness of the chest, hypotension, etc.), thromboembolic events (thromboembolism, pulmonary embolism), development of neutralizing antibodies (inhibitors), etc.; **AND**
- Any increases in dose must be supported by an acceptable clinical rationale (i.e., weight gain, half-life study results, increase in breakthrough bleeding when patient is fully adherent to therapy, etc.); **AND**
- The cumulative amount of medication(s) the patient has on-hand will be taken into account when authorizing. The authorization will allow up to 5 doses on-hand for the treatment of acute bleeding episodes as needed for the duration of the authorization; **AND**

Routine prophylaxis of bleeding

- Renewals will be approved for a 12-month authorization period; **AND**
- Patient has demonstrated beneficial response to therapy (i.e., the frequency of bleeding episodes has decreased from pre-treatment baseline)

VII. Dosage/Administration

Indication	Dose
Routine prophylaxis of bleeding in patients with congenital factor XIII A-subunit deficiency	Administer 35 international units (IU) per kilogram body weight once monthly to achieve a target trough level of FXIII activity at or above 10% using a validated assay.

VIII. Billing Code/Availability Information

HCPCS & NDC:

Drug	Manufacturer	J-Code	1 Billable Unit Equiv.	Vial Size	NDC
Tretten	Novo Nordisk	J7181	1 IU	Unassigned size	00169-7013-xx

IX. References

1. Tretten [package insert]. Bagsvaerd, Denmark; Novo Nordisk; June 2020. Accessed May 2025.
2. MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Selected Disorders of the Coagulation System. Revised April 11, 2024. National Hemophilia Foundation. MASAC Document #284; April 2024. Available at: <http://www.bleeding.org>. Accessed May 2024.
3. Guidelines for the Management of Hemophilia. 3rd Edition. World Federation of Hemophilia 2020. Available at: <https://www1.wfh.org/publications/files/pdf-1863.pdf>. Accessed May 2024.
4. Graham A1, Jaworski K. Pharmacokinetic analysis of anti-hemophilic factor in the obese patient. Haemophilia. 2014 Mar;20(2):226-9.
5. Croteau SE1, Neufeld EJ. Transition considerations for extended half-life factor products. Haemophilia. 2015 May;21(3):285-8.
6. Mingot-Castellano, et al. Application of Pharmacokinetics Programs in Optimization of Haemostatic Treatment in Severe Hemophilia a Patients: Changes in Consumption, Clinical Outcomes and Quality of Life. Blood. 2014 December; 124 (21).
7. MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors. Revised April 27, 2022. National Hemophilia Foundation. MASAC Document #267; April 2022. Available at: <http://www.bleeding.org>. Accessed May 2024.
8. Rayment R, Chalmers E, Forsyth K, et al. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. B J Haem:190;5,Sep2020. <https://doi.org/10.1111/bjh.16704>. Accessed May 2023.
9. Palmetto GBA. Local Coverage Article: Billing and Coding: Guidance for Anti-Inhibitor Coagulant Complex (AICC) National Coverage Determination (NCD) 110.3 (A56065). Centers for Medicare & Medicaid Services Inc. Updated on 11/14/2022 with effective date 11/24/2022. Accessed May 2024.
10. Novitas Solutions, Inc. Local Coverage Article: Billing and Coding: Hemophilia Factor Products (A56433). Centers for Medicare & Medicaid Services Inc. Updated on 09/29/2023 with effective date 10/01/2023. Accessed May 2024.
11. First Coast Service Options, Inc. Local Coverage Article: Billing and Coding: Hemophilia Factor Products (A56482). Centers for Medicare & Medicaid Services Inc. Updated on 09/29/2023 with effective date 10/01/2023. Accessed May 2024.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
D68.2	Hereditary deficiency of other clotting factors

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan

Medicare Part B Covered Diagnosis Codes		
Jurisdiction	NCD/LCA/LCD Document (s)	Contractor
J,M	A56065	Palmetto GBA
H,L	A56433	Novitas Solutions, Inc.
N	A56482	First Coast Service Options, Inc.

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA,
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale:

Tretten was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Tretten

according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.