Clinical Policy: Antithrombin III (ATryn, Thrombate III)

Reference Number: CP.PHAR.564
Effective Date: 03.01.22
Last Review Date: 02.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following are antithrombin products requiring prior authorization: antithrombin III, human (Thrombate III®) and antithrombin, recombinant (ATryn®).

FDA Approved Indication(s)

ATryn is indicated for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients.

Thrombate III is indicated in patients with hereditary antithrombin deficiency for:

- Treatment and prevention of thromboembolism
- Prevention of peri-operative and peri-partum thromboembolism

Limitation(s) of use: ATryn is not indicated for treatment of thromboembolic events in hereditary antithrombin deficient patients.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that ATryn and Thrombate III are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hereditary Antithrombin Deficiency (must meet all)**:**

1. Diagnosis of hereditary antithrombin deficiency;
2. Prescribed by or in consultation with a hematologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Request is for Thrombate III for the treatment or prevention of thromboembolism;
   b. Request is for prevention of peri-operative or peri-partum thromboembolism.

Approval duration:
Acute thrombosis or peri-operative/peri-partum prevention: 3 months
Prevention:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Hereditary Antithrombin Deficiency (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy.

Approval duration:
Acute thrombosis or peri-operative/peri-partum prevention: 3 months
Prevention:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents;

B. Disseminated intravascular coagulation (DIC).

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

DIC: disseminated intravascular coagulation
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to goat and goat milk proteins (*ATryn only*)
- Boxed warning(s): none reported

Appendix D: General Information

- In addition to the FDA-approved indications, antithrombin has been suggested for treatment of patients with DIC associated with trauma or sepsis. However, 2009 British guidelines for the diagnosis and management of DIC do not recommend antithrombin in patients with DIC without further prospective evidence in randomized controlled trials. More recent studies have not found clear benefit of antithrombin in treatment of DIC. A 2016 Cochrane review of antithrombin administration in critically ill patients concluded that there is insufficient evidence to support its use in any category of such patients, including those with sepsis and DIC. A 2022 statement from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) on sepsis-induced coagulopathy in the management of sepsis concluded that although antithrombin is a candidate for anticoagulation, it has not proven to be effective with robust evidence, and future trials are warranted.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Antithrombin III [human] (Thrombate III)	Individualize dose to achieve antithrombin level of 80% to 120% of normal human plasma. Loading dose (IV infusion): 120% - baseline % x body weight (kg) / 1.4%	Varies per baseline and target antithrombin levels

Drug Name	Dosing Regimen	Maximum Dose
	Adjustment (as needed, IV infusion): Target % - trough % x body weight (kg) / 1.4% Maintenance: Loading dose x 0.6 IV every 24 hours as needed	
Antithrombin [recombinant] (ATryn)	Treatment goal is to restore and maintain functional antithrombin activity levels between 80% - 120% (0.8 - 1.2 IU/mL) of normal. For surgical patients: *Loading dose (IV infusion):* 100% - baseline % x body weight (kg) / 2.3% *Maintenance (IV infusion):* 100% - baseline % x body weight (kg) / 10.2% For pregnant women: *Loading dose (IV infusion):* 100% - baseline % x body weight (kg) / 1.3% *Maintenance (IV infusion):* 100% - baseline % x body weight (kg) / 5.4% Continue administration of ATryn until adequate follow-on anticoagulation has been established.	Varies per baseline and target antithrombin levels

VI. Product Availability

Drug Name	Availability
Antithrombin III [human] (Thrombate III)	Single-dose vial: approximately 500 units
Antithrombin [recombinant] (ATryn)	Single-dose vial: approximately 525 IU or 1,750 IU

VII. References

1. Thrombate III Prescribing Information. Research Triangle Park, NC: Grifols Therapeutics LLC; October 2021. Available at: www.thrombate.com. Accessed November 1, 2024.
2. ATryn prescribing information. Framingham, MA: GTC Biotherapeutics, Inc; December 2013. Available at: https://www.fda.gov/media/75529/download?attachment. Accessed November 1, 2024.
3. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol. 2009 Apr;145(1):24-33.
4. Allingstrup M, Wetterslev J, Ravn FB, Møller AM, Afshari A. Antithrombin III for critically ill patients. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD005370.
5. 5. Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001; 286:1869.

6. Iba T, Levi M, Thachil J, et al. Communication from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis on sepsis-induced coagulopathy in the management of sepsis. J Thromb Haemost. 2023;21(1):145-153.
7. Medical and Scientific Advisory Council (MASAC) of the National Bleeding Disorders (formerly National Hemophilia Foundation): Database of treatment guidelines. Available at: https://www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents. Accessed November 18, 2024.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J7196	Injection, antithrombin recombinant, 50 IU
J7197	Antithrombin III (human), per IU

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created, based on medical policy CP.MP.179 (to be retired).	10.29.21	02.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.06.22	
1Q 2023 annual review: no significant changes; references reviewed and updated.	11.08.22	02.23
1Q 2024 annual review: no significant changes; references reviewed and updated.	10.27.23	02.24
1Q 2025 annual review: for Commercial line of business, revised initial and continued approval durations for prevention from "6 months" to "6 months or to the member's renewal date, whichever is longer;" references reviewed and updated.	11.01.24	02.25

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.