Drug and Biologic Coverage Policy

Effective Date **12/15/2024**
Coverage Policy Number **8007**

Clotting Factors and Antithrombin

Table of Contents

Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

The Clotting Factors and Antithrombin coverage policy includes the following products:

- **Antithrombin III**
  - **Human plasma-derived:** Thrombate III®
  - **Recombinant:** ATryn®
- **Antihemophilic Factor Recombinant, porcine sequence:** Obizur™

NOTE: Each Clotting Factor product has unique indications and uses and are only approved for use as listed in the criteria below.

Clotting Factor products are considered medically necessary when the following criteria are met:

Product	Criteria for Use
ATryn [antithrombin III (recombinant)]	Prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient individuals
Obizur	Treatment for bleeding episodes in an adult when **BOTH** of the following are met: • Diagnosis of acquired hemophilia A that is confirmed by documentation of autoimmune inhibitory antibodies to human factor VIII

Product	Criteria for Use
[antihemophilic factor (recombinant, porcine sequence)]	• Individual does NOT have congenital hemophilia A or von Willebrand disease
Thrombate III [antithrombin III (human)]	Treatment of an individual with hereditary antithrombin III deficiency for **EITHER** of the following: • Treatment and prevention of thromboembolism • Prevention of peri-operative and peri-partum thromboembolism

Clotting Factor products are considered experimental, investigational, or unproven for any other use.

Clotting Factors products are considered medically necessary for continued use when the individual continues to meet the initial criteria.

Initial and reauthorization is up to 12 months unless otherwise stated.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Clotting Factors or Antithrombin.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

General Background

Obizur (antihemophilic factor [recombinant, porcine sequence])	Obizur, Antihemophilic Factor (Recombinant), Porcine Sequence, is a recombinant DNA derived, antihemophilic factor indicated for the treatment of bleeding episodes in adults with acquired hemophilia A. Limitations of Use: • Safety and efficacy of Obizur has not been established in patients with baseline anti-porcine factor VIII inhibitor titer greater than 20 BU. • Obizur is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.

Professional Societies/Organizations for Management of Hemophilia A
The National Hemophilia Foundation (NHF) Medical and Scientific Advisory Council (MASAC) has recommendations concerning products used for the treatment of hemophilia and other bleeding disorders. It is noted that recombinant Factor VIII products are the recommended treatment of choice for patients with hemophilia A. The MASAC recommendations regarding plasma-derived Factor VIII products state that improved viral-depleting processes and donor screening practices have greatly reduced the risk of transmission and human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C virus (HCV). (MASAC, 2018)

Antithrombin Deficiency

Antithrombin (AT) is a natural anticoagulant that inhibits thrombin, factor Xa, and other enzymes. AT deficiency can be either inherited or acquired. Congenital AT deficiency is an autosomal dominant trait with an incidence of 1:2,000 to 1:5,000. Type 1 AT deficiency is a quantitative reduction in AT and Type II is a qualitative impairment. Normal plasma AT activity is 80-120% and 40-50% activity is considered a clinically important deficiency. (Pal, 2010)

Exogenous AT-III (human) is derived from pooled human plasma and must be administered intravenously. Antithrombin III clotting factor complexes are rapidly removed from the circulation by binding to a specific receptor present on hepatocytes. The elimination half-life of AT-III (human) is approximately two to three days. However, the half-life may be decreased following surgery, hemorrhage or acute thrombosis, and during

concurrent use of heparin. Recombinant antithrombin is produced through genetically engineered goat milk. Recombinant antithrombin has a shorter half-life and is cleared more rapidly compared to human plasma-derived antithrombin.

FDA Approved Products for Antithrombin Deficiency

Brand Name	Approved Indication(s)
ATryn (antithrombin [recombinant])	ATryn is a recombinant antithrombin indicated for the prevention of peri-operative and peri-partum thromboembolic events in hereditary antithrombin deficient patients. It is not indicated for treatment of thromboembolic events in hereditary antithrombin deficient patients.
Thrombate III (antithrombin III [human])	Thrombate III is a human antithrombin (AT) indicated in patients with hereditary antithrombin III deficiency for: • Treatment and prevention of thromboembolism • Prevention of peri-operative and peri-partum thromboembolism

Recommended Dosing

FDA Recommended Dosing

- **ATryn (recombinant antithrombin)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

  - For intravenous use only after reconstitution.
  - The dosage of ATryn is individualized for each patient. Treatment goal is to restore and maintain functional antithrombin (AT) activity levels between 80% - 120% (0.8 - 1.2 IU/mL) of normal.
  - Administer loading dose as a 15-minute intravenous infusion immediately followed by continuous infusion of the maintenance dose.

	Loading Dose (IU)		Maintenance Dose (IU/hour)	
Surgical Patients	$\frac{(100 - \text{baseline AT activity})}{2.3}$	x Body Wt (kg)	$\frac{(100 - \text{baseline AT activity})}{10.2}$	x Body Wt (kg)
Pregnant Women	$\frac{(100 - \text{baseline AT activity})}{1.3}$	x Body Wt (kg)	$\frac{(100 - \text{baseline AT activity})}{5.4}$	x Body Wt (kg)

  - AT activity monitoring is required for proper treatment. Check AT activity once or twice per day with dose adjustments made according to table below.

Initial Monitor Time	AT Level	Dose Adjustment	Recheck AT Level
2 hours after initiation of treatment	< 80%	Increase 30%	2 hours after each dose adjustment
	80% to 120%	None	6 hours after initiation of treatment or dose adjustment
	> 120%	Decrease 30%	2 hours after each dose adjustment

  - Continue administration of ATryn until adequate follow-on anticoagulation has been established.

- **Obizur (antihemophilic factor [recombinant], porcine sequence)**
  ***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.
- Initial dose of Obizur is 200 units per kg.
- Titrate dose and frequency of administration based on factor VIII recovery levels and individual clinical response.

➢ **Thrombate III (human antithrombin III)**

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

- For intravenous use after reconstitution only.
- Individualize dose to achieve AT level of 80 % to 120 % of normal human plasma.

Dose	Target AT Level	Dose (Units)	Monitor AT Level
Loading	120% of normal	120% - baseline % x body weight (kg) divided by 1.4%	• baseline • 20 minutes (peak) post-injection • 12 hours post-injection • pre-injection (trough)
Adjustment (as needed)	80% to 120% of normal	Target % - trough % x body weight (kg) divided by 1.4%	• 20 minutes (peak) post-injection • at least every 12 hours post-injection • pre-injection (trough)
Maintenance (every 24 hours as needed)	80% to 120% of normal	Loading Dose x 0.6	• approximately every 24 hours, as needed

Drug Availability

Product	Availability
ATryn	Supplied in a sterile lyophilized powder for reconstitution containing approximately 525 IU/vial.
Obizur	Supplied in single-use vials containing nominally 500 units per vial.
Thrombate III	Supplied in a kit containing one single-use vial of Thrombate III lyophilized powder containing approximately 500 units, one vial of Sterile Water for Injection, USP, one sterile double-ended transfer needle, and one sterile filter needle.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J7188	Injection, factor VIII (antihemophilic factor, recombinant), (Obizur), per IU
J7196	Injection, antithrombin recombinant, 50 IU
J7197	Antithrombin III (human), per IU

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Revision Details

Type of Revision	Summary of Changes	Date
Selected Revision	**Removed** from the policy: Adynovate, Eloctate, Esperoct, Jivi, Advate, Afstyla, Kogenate, Kovaltry, Novoeight, Nuwiq, Recombinate, Xyntha, Hemofil M, Alphanate, Humate-P, Koate, and Wilate. All were relocated to new policy, Hemophilia - Factor VIII Products (IP0618). Mononine was	12/15/2024

	discontinued by the manufacturer and also removed from the policy. **Coding Information:** **Removed** HCPCS codes: J7178, J7182, J7183, J7185, J7186, J7187, J7189, J7190, J7192, J7198, J7199, J7204, J7205, J7207, J7208, J7209, J7210, J7211	

The policy effective date is in force until updated or retired.

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