



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Antithrombin III (Human)
(Thrombate III®)**

Effective Date 9/15/2010
Next Review Date..... 9/15/2011
Coverage Policy Number 6016

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Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), 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 participant'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 participant's benefit plan document **always supercedes** 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 group 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. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers antithrombin III (human) (Thrombate III®) as medically necessary for the treatment of individuals with hereditary antithrombin III deficiency in connection with surgical procedures, obstetrical procedures, or thromboembolism.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity and previous response to Antithrombin III (Human) (Thrombate III®) therapy for the condition being addressed.

FDA Approved Indications

Thrombate III is indicated for the treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism. Subjects with AT-III deficiency should be informed about the risk of thrombosis in connection with pregnancy and surgery and about the inheritance of the disease. The diagnosis of hereditary antithrombin III (AT-III) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma AT-III levels, and the exclusion of acquired deficiency. AT-III in plasma may be measured by amidolytic assays using synthetic chromogenic substrates, by clotting assays, or by immunoassays. The latter does not detect all hereditary AT-III deficiencies. The AT-III level in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. Plasma levels of AT-III are lower in neonates than adults, averaging approximately 60% in normal term

infants. AT-III levels in premature infants may be much lower. Low plasma AT-III levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with Thrombate III of neonates be discussed with an expert on coagulation.

FDA Recommended Dosing

The exact loading and maintenance doses and dosing intervals for AT-III (human) should be individualized for each patient, based on the individual clinical conditions, response to therapy, and actual plasma AT-III levels achieved. The dosing recommendations provided below should be used only as a general guideline for therapy. As a general recommendation, the following therapeutic program may be utilized as a starting program for treatment, but the program should be modified based on the actual plasma AT-III levels achieved.

An initial loading dose of AT-III (human) calculated to elevate the plasma AT-III level to 120% may be given, assuming an expected rise over the baseline plasma AT-III level of 1.4% (functional activity) per international unit (IU) per kilogram (kg) of AT-III (human) administered. The initial dose should be determined on an individual basis based on the pre-therapy plasma AT-III level and can be calculated according to the following formula:
Dose = [(desired AT-III level (as % of normal) - baseline AT-III level (as % of normal)) body weight (in kg)]
1.4. Administration of the entire dose in 10 to 20 minutes is generally well-tolerated, but the rate of administration should be adapted to the response of the individual patient.

Recovery may vary, and subsequent doses can be calculated based on the recovery of the first dose. It is recommended to measure pre-infusion and 20 minutes post-infusion (peak) plasma AT-III levels following the initial loading dose, plasma AT-III level after 12 hours, then preceding the next infusion (trough level). Subsequently, measure AT-III levels preceding and 20 minutes after each infusion until predictable peak and trough levels have been achieved, generally between 80%–120%. Plasma levels between 80%–120% may be maintained by administration of maintenance doses of 60% of the initial loading dose, administered every 24 hours. Adjustments in the maintenance dose and/or interval between doses should be made based on actual plasma AT-III levels achieved. In some situations (e.g., following surgery, hemorrhage or acute thrombosis, and during concurrent use of heparin), the half-life of AT-III (human) may be decreased. In such situations, plasma AT-III levels should be monitored more frequently and AT-III (human) may be administered more frequently as necessary.

The duration of therapy depends on the indication for treatment, type and extent of surgery, patient's medical condition, past history, and the judgment of the physician. Treatment is usually continued for two to eight days. In each of these situations, the concomitant use of heparin should be based on the physician's medical judgment. In some circumstances (e.g., during pregnancy), more prolonged administration may be needed. Also, when treatment is given in conjunction with surgery or during prolonged immobilization, it is recommended that AT-III (human) therapy be continued until the patient is fully mobilized.

Drug Availability

Antithrombin III (Human), Thrombate III is supplied in the following single use vials with the potency in international units stated on the label of each vial. A suitable volume of Sterile Water for Injection, USP, a sterile double-ended transfer needle, and a sterile filter needle are provided – 500IU/10mL and 1000IU/20mL. .

General Background

Pharmacology

Exogenous AT-III (human) is derived from pooled human AT 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.

Clinical Efficacy

In clinical studies of AT-III (human), none of the 13 patients with hereditary AT-III deficiency and histories of thromboembolism treated prophylactically on 16 separate occasions with AT-III (human) for high thrombotic risk situations (11 surgical procedures, five deliveries) developed a thrombotic complication. Heparin was also administered in three of the 11 surgical procedures and all five of the deliveries. Eight patients with hereditary

AT-III deficiency were treated therapeutically with AT-III (human) as well as heparin for major thrombotic or thromboembolic complications, with seven patients recovering. Treatment with AT-III (human) reversed heparin resistance in two patients with hereditary AT-III deficiency that were being treated for thrombosis or thromboembolism.

Although long-term prophylaxis against the development of thrombotic complications may be required in patients with hereditary AT-III deficiency, AT-III (human) is usually not used, whether or not a high-risk situation, such as a surgical or obstetrical procedure, exists. Usually, a coumadin- or indandione-derivative anticoagulant (e.g., warfarin) is used for this purpose. However, these anticoagulants should not be administered during the first trimester of pregnancy, and some clinicians recommend that they not be used at all during pregnancy. Heparin is usually used instead, but may be ineffective when concentrations of endogenous AT-III are low. Therefore, long-term prophylactic use of AT-III (human) may be required if heparin alone fails to produce adequate anticoagulation.

Adverse Reactions/Warnings

Side effects of AT-III (human) that have been reported in clinical trials include dizziness, chest tightness, nausea, foul taste in mouth, chills, cramps, shortness of breath, chest pain, film over eye, light-headedness, bowel fullness, hives, fever, oozing and hematoma formation. If these side effects occur, they may be abated by slowing or temporarily discontinuing the infusion.

Concurrent administration of heparin and AT-III (human) increases the anticoagulant effect of both medications because AT-III (human) is the primary cofactor required for heparin to exert an anticoagulant effect. Reduced dosage of heparin is recommended during treatment with AT-III (human) in order to avoid bleeding. Heparin also decreases the half-life of AT-III (human).

Antithrombin III (human) is made from human plasma and may contain infectious agents that can cause disease, such as viruses. Although many measures have been taken to reduce the risk that this product will transmit an infectious agent, this product can still potentially transmit disease.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary for the treatment of individuals with hereditary antithrombin III deficiency in connection with surgical procedures, obstetrical procedures or thromboembolism:

HCPCS Codes	Description
J7197	Antithrombin III (human), per IU

ICD-9-CM Diagnosis Codes	Description
289.81	Primary hypercoagulable state

References

1. McEvoy GK, ed. AHFS 2010 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc. 2010.
2. Talecris Biotherapeutics, Inc. Thrombate III® (antithrombin III [human]) package insert. Research Triangle Park, NC: Talecris Biotherapeutics, Inc. May 2009.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	7/15/2008	6016	Antithrombin III (Human) (Thrombate III®)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.