Reference number(s)
4371-A

STANDARD MEDICARE PART B MANAGEMENT

THROMBATE III (Antithrombin III [Human])

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
   1. Indicated in patients with hereditary antithrombin deficiency for treatment and prevention of thromboembolism
   2. Indicated in patients with hereditary antithrombin deficiency for prevention of peri-operative and peri-partum thromboembolism

B. Compendial Uses
   1. Acquired antithrombin III deficiency
   2. Heparin resistance prior to and during cardiopulmonary bypass (CPB)
   3. Sickle cell-thalassemia, treatment of chronic leg ulcers

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. **Hereditary Antithrombin Deficiency**
   1. Authorization of 12 months may be granted for treatment of hereditary antithrombin deficiency when the requested medication will be used for any of the following indications:
      i. Treatment of thromboembolism
      ii. Prevention of thromboembolism
   2. Authorization of 1 month may be granted for the treatment of hereditary antithrombin deficiency when the requested medication will be used for any of the following indications:
      i. Prevention of peri-operative (i.e., surgical procedures) thromboembolism
      ii. Prevention of peri-partum (i.e., obstetrical procedures) thromboembolism

B. **Acquired Antithrombin Deficiency**
Authorization of 6 months may be granted for treatment of acquired antithrombin deficiency when both of the following criteria is met:
1. The member has a condition associated with low levels of antithrombin III (e.g., disseminated intravascular coagulation (DIC) associated with sepsis or trauma, liver failure, asparaginase-induced antithrombin deficiency)
2. The requested medication will be used for the treatment or prophylaxis of thromboembolism.

C. **Heparin Resistance**
Authorization of 1 month may be granted for treatment of heparin resistance prior to and during cardiopulmonary bypass (CPB).

D. **Sickle cell beta thalassemia**
Authorization of 3 months may be granted for treatment of chronic leg ulcers in patients with sickle cell beta thalassemia.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with Thrombate III
B. Thrombate III is being used to treat hereditary antithrombin deficiency (excluding prevention of peri-operative and peri-partum thromboembolism), acquired antithrombin deficiency, or sickle cell beta thalassemia.
C. The member is receiving benefit from therapy.

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Thrombate III.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Thrombate III are covered in addition to the following:
1. Acquired antithrombin III deficiency
2. Heparin resistance prior to and during cardiopulmonary bypass (CPB)

3. Sickle cell-thalassemia, treatment of chronic leg ulcers

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using Thrombate III to treat acquired antithrombin III deficiency be found in a study of by Eisele et al. Antithrombin III (AT III) therapy was safe and well tolerated in 42 patients with severe SEPSIS who were receiving standard supportive care and antimicrobial therapy. The endpoints, safety and 30-day all-cause mortality relative to placebo established in this double-blind, phase II, multicenter, multinational clinical trial showed a positive trend for the group that received AT III with the following results: AT III was safe and well tolerated; an overall 39% reduction in 30-day all-cause mortality (41% mortality in the placebo group (9 out of 22) compared to only 25% mortality (5 out of 20) in AT III patients); shorter stay in the ICU; and improved APACHE (Acute Physiology and Chronic Health Evaluation II, multiple organ failure, organ system failure) scores. Patients were randomized to receive an intravenous loading dose of 3000 International Units (IU) AT III, or placebo, administered over approximately 1 hour, followed by a maintenance dose of 1500 IU every 12 hours for 5 days. An author conducted meta-analysis of two other double-blind, placebo-controlled trials involving 122 patients (62 placebo, 60 AT III) with severe sepsis showed a similar 22.9% reduction in 30-day all-cause mortality. Additionally, antithrombin III (ATIII) was safe and effective in a 40-year-old burn patient with a high incidence of hypercoagulability and thrombosis (Kowal-Vern, et al). The patient presented with third degree burns covering over 68% of his body. He also had a comminuted femoral fracture and C5-C6 subluxation as a result of a motor vehicle accident and a baseline ATIII level of 45%. He was treated with standard burn wound care and received a total of nine ATIII concentrate infusions within the first four days. The plasma level of ATIII was maintained at 175% or higher, with a dose determined by the following formula: [(desired ATIII level %-patient ATIII level %) x (admission weight, kg)] divided by 1.4. The patient tolerated ATIII treatment with no excessive bleeding and no drop in blood pressure. The authors concluded that ATIII treatment in burn patients is beneficial and may be crucial to increase vascularization of subcutaneous tissue, as well as inhibit anti-inflammatory protease. They also state that ATIII therapy should be initiated as early as possible within the first 24 hours, during the time of low plasma ATIII levels.

Support for using Thrombate III to treat heparin resistance prior to and during cardiopulmonary bypass can be found in a study of 22 patients by Rossi and colleagues. In a study of 22 patients with unstable angina, antithrombin III (ATIII) allowed for adequate anticoagulation during elective coronary artery bypass surgery. It also avoided the activation of the coagulation cascade. Patients were randomly divided into group A and received ATIII 3000 IU and heparin 300 units/kilogram (U/kg), or group B, and received only heparin 300 U/kg. Heparin 10000 units was included in the bypass circuit of all patients. Activated coagulation time (ACT) was monitored throughout the surgery and maintained at 480 seconds or greater. Prothrombin time (PT), activated prothrombin time (aPTT), and fibrinogen and platelets were monitored. Whole blood samples were also obtained to monitor ATIII, thrombin-antithrombin complexes (TAT), fragment 1.2 of prothrombin (F 1.2), and split products of the cross-linked fibrin (D-dimers). Additional heparin was required in group B to maintain ACT values, but not in group A (p less than 0.05). The need for protamine sulfate to neutralize heparin was significantly lower in group A (p less

than 0.05). Both groups had similar results in PT, aPTT, fibrinogen values, and platelet levels. TAT and F 1.2 increased significantly in group B (p less than 0.01), however differences in D-dimers were not significant. The authors concluded that patients who received ATIII showed a better intraoperative and postoperative coagulation pattern and expression of a more correct functioning of the hemostatic balance. The high cost of ATIII should be considered, as should the costs associated with blood transfusions and surgical reexploration.

Support for using Thrombate III to treat chronic leg ulcers associated with sickle cell thalassemia can be found in a study by Cacciola and colleagues. The combination of antithrombin III concentrate as 1000 units intravenously every 48 hours for 2 weeks, followed by the same dose every 72 hours for 4 further weeks plus calcium heparin 150 units/kg subcutaneously once daily for 6 weeks was effective in increasing antithrombin III levels and producing clinical improvement of chronic leg ulcers in patients with sickle cell beta-thalassemia in an uncontrolled study. The reduced levels of antithrombin III in plasma, as well as elevated levels of fibrinopeptide A, observed prior to treatment were suggestive of hypercoagulation via chronic thrombin activation in these patients. Antithrombin III concentrate was administered due to suspected acquired antithrombin III deficiency. All patients in this study had been refractory either to conventional therapy or anticoagulants. Controlled clinical studies are needed to further assess the efficacy of antithrombin III concentrate in treating refractory leg ulcers in patients with sickle cell beta-thalassemia.

VI. REFERENCES

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5. Kowal-Vern A, McGill V, Walenga JM, et al: Antithrombin III concentrate in the acute phase of thermal injury. Burns 2000; 26:97-101.
6. Rossi M, Martinelli L, Storti S, et al: The role of antithrombin III in the perioperative management of the patient with unstable angina. Ann Thorac Surg 1999; 68:2231-2236.
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