Thrombate III Disease & Product Overview

1. Introduction

Hello—and welcome to a unique interactive presentation that will inform you about hereditary antithrombin deficiency and a unique product—Thrombate III—the only FDA-approved therapy for patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

The Thrombate III Disease and Product Overview is designed to impart the following key information:
- The role of antithrombin in normal physiology
- The current state of knowledge of hereditary antithrombin deficiency and the seriousness of the condition
- Knowledge of the protocol for diagnosing the disorder through patient and family history and laboratory testing
- The options for treating patients with hereditary antithrombin deficiency for both the short- and long-term
- The nature of Thrombate III and its special role in patient management

Thank you for your interest in Thrombate III.

THROMBATE III® has demonstrated a low occurrence of side effects. In clinical studies with THROMBATE III®, the most common side effects were dizziness, chest tightness, nausea, and a foul taste in the mouth. As with all plasma-derived therapeutics, the potential to transmit infectious agents, such as viruses, cannot be totally eliminated. Individuals who receive infusions of blood or blood plasma may develop signs and/or symptoms of some viral infections, particularly hepatitis C.

Please see full Prescribing Information for Thrombate III® at www.thrombate.com.
2. MOA

Thrombate III is human antithrombin and its mechanism of action is the same as native antithrombin. Antithrombin is a direct thrombin inhibitor.\(^1\) Antithrombin is also a potent serine protease inhibitor with activity in other physiological processes.\(^1\)

To understand the role of antithrombin, let’s look at the coagulation cascade.

Manufactured in the liver, antithrombin is the most important serine protease inhibitor of coagulation\(^2\) and plays a critical role in maintaining hemostasis.\(^2\)

Can you recall how the intrinsic and extrinsic pathways come together at the activation of factor X?

The cascade is a series of enzymatic reactions initiated by tissue factor in the extrinsic pathway and high molecular weight kininogen in the intrinsic pathway.\(^3\)

The two pathways converge into a common pathway. The common pathway culminates in the activation of crosslinked fibrin polymer, necessary to the maintenance of a clot.\(^3\)

The common pathway starts with the activation of factor X. Factor Xa, along with calcium ions, phospholipids and activated factor V form a prothrombinase complex on platelet membranes. This complex catalyzes the conversion of prothrombin to its active form, thrombin (also called factor IIa).\(^3\)
Thrombin is the enzyme that triggers the conversion of inactive fibrinogen into soluble fibrin monomer. Fibrin monomer is then converted to a stable fibrin polymer, which binds aggregated platelets into a clot. Antithrombin inactivates factor Xa and thrombin by binding irreversibly to them. Thus, it puts a brake on the accelerating coagulation process at two points. Combinations of antithrombin and thrombin and factor Xa are broken down by the liver.

The reduction in available thrombin caused by antithrombin reduces the amount of fibrinogen converted into a fibrin polymer. The reduction in fibrin directly inhibits clot formation.

Heparin accelerates the anticoagulant activity of antithrombin by approximately one thousand fold compared to antithrombin alone. Without antithrombin, heparin has no anticoagulant effect.
3. Hereditary Antithrombin Deficiency

Hereditary antithrombin deficiency was first identified in 1965 in a Norwegian family.\textsuperscript{5} It affects anywhere from one in 2 thousand to one in 5 thousand people in the general population.\textsuperscript{1} To put this in perspective, the incidence of hereditary antithrombin deficiency is at least three times that of hemophilia A—and maybe greater.\textsuperscript{6}

Hereditary antithrombin deficiency is an autosomal dominant condition\textsuperscript{1} that is not restricted to any particular ethnic group\textsuperscript{7} and is expressed equally in males and females.\textsuperscript{1,7,8}

Antithrombin is present in the circulation at about 12.5 milligrams per deciliter.\textsuperscript{1} A deficiency of antithrombin allows activated procoagulant proteins to circulate for a longer time. This increases the risk of thrombosis, primarily deep vein thrombosis or DVT for short.\textsuperscript{8} A 40% to 60% reduction in antithrombin is associated with an increased risk of spontaneous episodes of thrombosis and pulmonary embolism.\textsuperscript{1}

Hereditary antithrombin deficiency presents the highest risk of thrombosis among inherited thrombophilias. This chart displays the risks of thrombosis relative to the normal population. Note that hereditary antithrombin deficiency presents 4 times the risk of thrombosis as factor V Leiden, the most common hereditary thrombophilia.\textsuperscript{8}

The arithmetic of risk illuminates how serious hereditary antithrombin deficiency is. Of all patients with hereditary antithrombin deficiency:

- More than 85% will have at least one thrombotic episode by age 50 years\textsuperscript{1}
- Thrombosis will recur in about 60%\textsuperscript{1}
- And in many cases, no precipitating factor can be identified for thrombosis or pulmonary embolism.\textsuperscript{1}

Precipitating events that increase the risk of thrombosis include surgical and obstetrical procedures. It’s not unusual for the first thrombosis in antithrombin-deficient women to appear during pregnancy.
Pregnancy is a thrombophilic condition. The risk of venous thromboembolism increases 7-10 fold during pregnancy and is greatest after delivery. The incidence of thrombosis for women with hereditary antithrombin deficiency has been reported to be 70% during pregnancy.

Patients with hereditary antithrombin deficiency are also at increased risk of thrombosis during surgery. Thrombate III is the only treatment indicated to restore hemostasis in these patients. Thrombate III does not increase the risk of bleeding.

Thrombate III is also indicated as therapy for patients with thromboembolism. It stabilizes hemostasis during treatment and has been shown to reverse heparin resistance.
4. Patient Types

Hereditary antithrombin deficiency is autosomal dominant. This genetic tree represents the first family diagnosed with hereditary antithrombin deficiency. Those who experienced deep vein thrombosis had antithrombin levels ranging from 40 to 60 percent of normal. First events occurred between 10 and 25 years of age.

There are over 250 known phenotypes. Due to the large number of phenotypes, the results from genetic testing are of limited diagnostic value.

There are 2 primary types of hereditary antithrombin deficiency.

Type I, in which patients do not produce enough antithrombin. A 40% to 60% reduction in AT is associated with an increased risk of spontaneous episodes of thrombosis and pulmonary embolism.

Type II, in which the antithrombin produced is defective in a way that affects its function either seriously or subclinically.  

- Subtype IIa has defects in the reactive thrombin binding site and carries a high risk of thrombosis
- Subtype IIb has defects in the heparin binding site and a low risk of thrombosis
- Subtype IIc has multiple defects and a high risk of thrombosis

Type II is more common than type I.

The complexity of antithrombin mutations creates a dilemma for doctors because the life-long course of health for these patients is often unpredictable.
5. Diagnosing Hereditary Antithrombin Deficiency

The many mutations that comprise hereditary antithrombin deficiency make diagnosis a complex process. A thorough diagnostic procedure should include:

- Family history of thrombosis
- Personal history of thrombotic events
- Plasma antithrombin level tests
- Elimination of the causes of acquired antithrombin deficiency, including:
  - Decreased synthesis due to liver disease, malnutrition, or neonatal status. Neonates normally have lower antithrombin levels.
  - Increased excretion due to kidney problems, bowel disease, and other conditions that result in protein loss.
  - Accelerated consumption due to DIC associated with sepsis, shock, or trauma, as well as surgery, burns, pre-eclampsia, or hemolytic uremic syndrome
  - Drug therapies, including heparin,
  - L-asparaginase, and oral estrogen contraceptives.
  - Extracorporeal circulation for plasmapheresis, hemodialysis, and cardiopulmonary bypass.
  - And other causes, including conditions such as lupus, post-prothrombin complex, malignancies, and advancing age.

However, unless other family members have been definitively diagnosed with antithrombin deficiency, the process cannot rule out other hereditary thrombophilias or multiple thrombophilias until laboratory test results are returned.

One diagnostic protocol stratifies patients who have had a thrombotic event by the likelihood of their having thrombophilia. The risk of thrombophilia is moderate in patients who have had a thrombosis after turning 50 years of age, but also have other risk factors, such as use of oral contraceptives, but no known family history.

The high-risk group is defined as those patients with a thrombosis before 50 years of age, a recurrent thrombosis, or those who have a first-degree relative who has had an event before 50 years of age.

The distinction between low and high risk relies heavily on family history. However, the unpredictability of antithrombin mutations can render family history unrevealing. In the literature there is an illustrative case of an antithrombin deficient woman who suffered repeated thrombotic events beginning at age 20. Yet her father and 3 siblings, all of whom tested positive for antithrombin deficiency, had not experienced a single event up to the time the patient presented.
Consequently, the confirming step in a diagnosis of hereditary antithrombin deficiency is laboratory testing.

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Risk of Having a Thrombophilia</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of venous thromboembolic disease with known risk factors for thromboembolism and no family history of thromboembolism*</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Age older than 50 years, idiopathic first episode of venous thromboembolic disease, and no family history of thromboembolism*</td>
<td>Moderate</td>
<td>Resistance to activated protein C with a clotting assay that dilutes patient plasma in factor V-deficient plasma, or genetic test for factor V Leiden mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Genetic test for prothrombin G20210A mutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clotting assay for lupus anticoagulant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ELISA® for antiphospholipid antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma homocysteine level</td>
</tr>
<tr>
<td>Idiopathic venous thromboembolic disease before age 50 years or Recurrent thrombosis or Family history of thromboembolism*</td>
<td>High</td>
<td>All of the above and— Antithrombin assay (heparin cofactor assay) Protein C assay Protein S assay</td>
</tr>
</tbody>
</table>
6. Antithrombin Level Assays

Since family history may be unrevealing, a differential and definitive diagnosis of hereditary antithrombin deficiency depends largely on antithrombin level testing.

There are 2 types of antithrombin assay—immunologic assays using an antithrombin antigen and functional assays for either thrombin or factor Xa inhibition.\textsuperscript{10}

The most commonly used assay is the factor Xa inhibition assay\textsuperscript{14} because it has greater specificity than the thrombin assay.\textsuperscript{15}

In this assay, heparin and factor Xa are mixed with the patient's plasma and antithrombin inhibitory activity is determined by the rate of conversion of a chromogenic substrate. The activity rate correlates with a plasma antithrombin level.

Both types of assay have limitations of specificity, sensitivity, and repeatability. Consequently, an algorithm has been developed to interpret assay results.\textsuperscript{10}

**An Algorithm for Interpreting AT Laboratory Assays\textsuperscript{10}**

- **Doubtful Significance**
- **Perform AT Functional Assay**
  - **Normal**
    - AT Deficiency Unlikely
  - **Decreased**
    - Repeat AT Functional Assay on a New Specimen (Antigen Assay Also Helpful)
- **Decreased Functional and Antigenic AT**
  - Possible Type I AT Deficiency
    - Rule out acquired deficiency due to heparin therapy, liver disease, DIC, thrombosis, malignancy. Long-term therapy: malabsorption, nephrotic syndrome.
    - Family studies may be helpful to establish a diagnosis.
    - Genetic studies rarely performed due to large number of possible mutations.
  - **Type II AT Deficiency**
    - If further characterization required, genetic testing is necessary to distinguish subtypes.
    - **Ila** Mutations of reactive site (P2, I1, or I17 residue involved)
    - **IIb** Mutations of heparin binding site (lower thrombosis risk)
    - **IIc** Mutations of B2-domain 1C

The algorithm calls for performing one of the antithrombin functional assays on two different blood samples in order to confirm the results.\textsuperscript{1}

Following confirmation of the functional assay, the algorithm suggests that a positive antithrombin antigen assay be interpreted as confirmation of type I antithrombin deficiency and a negative antigen assay is confirmation of type II antithrombin deficiency. Genetic testing to determine the exact nature of the mutation is an option, but might have minimal impact on the clinical management of disease.\textsuperscript{10}
7. Patient Management

The purpose of patient management is to reduce the risk of thrombosis. Management falls into 2 categories:

Short-term treatment for high-risk situations and long-term management of patients who have had thrombosis

For short-term treatment:
One patient management scheme considers the life progression of patients with hereditary antithrombin deficiency.

- Evaluation of patient and family history
- Education and counseling
- Early diagnostic evaluation of children
- Appropriate treatment to reduce the risk of thrombosis

The focus of the scheme is on prevention of thrombosis in high-risk situations.16

Thrombate III has been proven to prevent thrombosis in these situations and is the only FDA-approved treatment for hereditary antithrombin deficiency. Acute care hospitals should have adequate supplies of Thrombate III on hand to meet patient needs.

For long-term treatment:
Oral anticoagulants can be considered for patients who have had thrombotic events. But, there is fundamental disagreement about the use and risks of long-term oral anticoagulants, such as Vitamin K inhibitors in these patients.17

Weighing all the factors—patient and family history, and lab test results—the best course of action may be to establish an individualized management program for each patient.
8. About Thrombate III®

Thrombate III is the only FDA-approved therapy for the treatment of patients with hereditary antithrombin deficiency. Thrombate III is concentrated human antithrombin fractionated from plasma.¹

Thrombate III is indicated for use in connection with surgical or obstetrical procedures or when patients suffer from thromboembolism. In clinical trials, Thrombate III was effective in preventing thrombosis in these high-risk situations.¹

Thrombate III is a potent hemostatic agent that restores the balance in hemostasis without increasing the risk of bleeding. However, when heparin is given with Thrombate III it is recommended to reduce the dosage of heparin to avoid bleeding.¹

Thrombate III is an important measure in preventing thrombosis in patients with hereditary antithrombin deficiency when they face surgical or obstetrical procedures.

Because Thrombate III has a high degree of purity, dosing is predictable. Purification removes other coagulation proteins. Thrombate III allows you to achieve target antithrombin levels easily and precisely, giving you control of hemostasis in patients at risk.

Thrombate III is safe. With more than 15 years on the market and over 100 million IUs administered, no report of virus transmission has ever been linked to Thrombate III. Pasteurization is used to inactivate enveloped and non-enveloped viruses. Thrombate III is purified to remove pro-inflammatory antibodies and cytokines.¹

Thrombate III has a low incidence of side effects, which include dizziness, chest tightness, nausea, and a foul taste in the mouth. Thrombate III has no known contraindications.¹

A complex fractionation process with 2 heparin affinity steps assures the quality of Thrombate III.

Talecris Biotherapeutics is a leader in plasma protein development and manufacture. Talecris is committed to maintaining a safe and reliable supply of Thrombate III.

In 2006, Talecris acquired 58 plasma collection centers to ensure a steady supply of materials.

And expanded manufacturing facilities are being built to meet the growing demand for Thrombate III.

Talecris is looking to the future through research into the role of antithrombin in human physiology and potential new uses for Thrombate III.
9. Thrombate III® vs. FFP

Thrombate III is indicated for patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.\textsuperscript{1}

Fresh frozen plasma, or FFP, is contraindicated if the specific coagulation factor is available as a concentrate.\textsuperscript{18,19}

Thrombate III is purified human antithrombin and completely predictable. It gives physicians precise control over dosing and allows treatment to achieve a target antithrombin level easily and accurately.

Let’s assess the characteristics of Thrombate III and FFP.

**Treatment With Thrombate III vs FFP**

<table>
<thead>
<tr>
<th>Category</th>
<th>Thrombate III®</th>
<th>FFP (fresh frozen plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>• Proven by clinical trial to reduce thrombotic events</td>
<td>• No clinical trials to prove reduction of thrombotic events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Usage based on empirical experience only</td>
</tr>
<tr>
<td>Dosing</td>
<td>• Concentrated antithrombin is predictable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Allows precise dosing</td>
<td>• Antithrombin levels unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No established dosing regimen</td>
</tr>
<tr>
<td>Safety Processing</td>
<td>• Highly purified from human plasma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pasteurized for virus inactivation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Purified to remove proinflammatory cytokines</td>
<td>• Unpurified human plasma product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No virus inactivation or removal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Contains proinflammatory antibodies and cytokines</td>
</tr>
<tr>
<td>Adverse events</td>
<td>• Rare; none consistently associated</td>
<td>• Consistently associated with TRALI and TACO</td>
</tr>
<tr>
<td>Side effects</td>
<td>• Low incidence</td>
<td>• Low incidence</td>
</tr>
<tr>
<td>Storage</td>
<td>• Should be refrigerated in:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Pharmacy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Operating room</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Blood bank</td>
<td>• Must be stored frozen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ordered from blood bank</td>
</tr>
<tr>
<td>Convenience</td>
<td>• 5-10 minutes to reconstitute with Sterile Water for Injection</td>
<td>• Up to 45 minutes to thaw, which can add costly time delays in the operating room</td>
</tr>
</tbody>
</table>

In clinical trials, Thrombate III was proven to reduce thrombotic events. As for FFP, there have been no clinical trials to prove it reduces thrombotic events. The use of FFP is based only on the empirical experience of physicians.
The concentrated antithrombin of Thrombate III is predictable and allows precise dosing. The antithrombin levels in FFP are unknown, and there is no established dosing regimen.

To ensure patient safety, Thrombate III is pasteurized for virus inactivation and purified to remove pro-inflammatory cytokines.

Adverse events are rare with Thrombate III and there is a low incidence of side effects.

FFP is an unpurified human plasma product with no virus inactivation or removal process. Also, FFP contains pro-inflammatory antibodies and cytokines.

While it has a low incidence of side effects, FFP is consistently associated with transfusion related acute lung injury, or TRALI, and transfusion associated cardiac overload, or TACO, both TRALI and TACO are serious adverse events.

Thrombate III should be refrigerated, and can be stored in the pharmacy, the operating room or the blood bank. In addition, Thrombate III only takes 5-10 minutes to reconstitute with Sterile Water for Injection.

FFP must be stored frozen and ordered from a blood bank. Because FFP is frozen it takes up to 45 minutes to thaw, which can add costly time delays.

Acute care hospitals should maintain an adequate supply of Thrombate III to meet patient needs.
10. Summary

Thrombate III is necessary therapy for patients with hereditary antithrombin deficiency. It should be readily available to meet emergent needs.

Remember:
• Thrombate III is Efficacious—proven efficacy for your patients.
• Thrombate III is predictable—giving you precise control over hemostasis.
• And Thrombate III is safe—pasteurized to inactivate viruses and purified to remove antigens and cytokines.\(^1\)

Along with its benefits for your patients, Thrombate III is convenient to use. It’s backed by the commitment of Talecris—a commitment you can trust.

Thrombate III is available through a network of specialty distributors. You can find out how to order Thrombate III at www.thrombate.com.

We encourage you to leave feedback about this program to help us determine future interactive directions.

Thank you for viewing the Thrombate III Disease and Product Overview.
**Dosing Information**

In general, it is desirable to raise the patient’s antithrombin level to normal (100%) and maintain this level for 2 to 8 days, depending on the indication for treatment, type and extent of surgery, patient’s medical condition and history, and physician’s judgment.

As a general recommendation, a starting treatment program includes:

An initial loading dose of Thrombate III calculated to elevate the plasma AT level to 120%. An initial increase in the plasma AT level to 120%, rather than 100%, is desirable to compensate for early declines following the initial loading dose.

Here’s how to calculate the loading dose:

1. First subtract the measured or physiologic antithrombin level from 120, and then divide the difference by 1.4. The result is the number of international units per kilogram of body weight needed to achieve a 120% of normal antithrombin level.

2. Then multiply that result by the patient’s weight in kilograms to obtain the number of units required for the initial loading dose of Thrombate III.

Thus, for a patient who weighs 70 kg and has a 57% antithrombin level, the loading dose is:

- (120 minus 57) divided by 1.4, which equals 45 IU per kg
- Then, 45 IU times 70 kg equals 3150 total international units

A baseline measurement of plasma AT levels should be obtained preinfusion. Level measurements should be taken 20 minutes postinfusion, every 12 hours postinfusion, and before the next infusion. Plasma levels between 80% and 120% may be maintained by administering 60% of the initial loading dose every 24 hours.

Adjustments in the maintenance dose and/or interval between doses should be made based on actual plasma AT levels achieved.
**Special Considerations**

The life of circulating Thrombate III can be significantly shortened following some surgeries, when there is hemorrhage or acute thrombosis, and after intravenous heparin administration. In these cases, additional monitoring is warranted and more frequent Thrombate III administration may be necessary.

**Reconstitution**

Aseptic technique should be carefully followed when reconstituting Thrombate III. Be sure to follow the detailed instructions as specified in the full Prescribing Information for Thrombate III.

Thrombate III is supplied in single use vials of 500 IU.

A volume of Sterile Water for Injection, a sterile double-ended transfer needle, a sterile filter needle, and dosing instructions are included with each vial.

For clinical questions about Thrombate III please contact Talecris Clinical Communications at **1-800-520-2807**.

Please see full Prescribing Information for Thrombate III at [www.thrombate.com](http://www.thrombate.com).