Understanding Hereditary Antithrombin Deficiency

Have You or a Family Member Had a Blood Clot?
Blood clots interrupt the flow of blood in the body and cause a variety of symptoms, such as pain, swelling, or weakness.

There are many different causes of blood clots. It is important to know if you have a condition that may cause you to have more blood clots in the future.

Some causes of blood clots are genetic and can run in families. One of these is hereditary antithrombin deficiency.

If you know you have hereditary antithrombin deficiency, you and your doctor can take steps to lower your risk of a blood clot during certain high-risk times.

A blood test recommended by your doctor is the only way to know if you have hereditary antithrombin deficiency.

If you have hereditary antithrombin deficiency, other members of your family may have the same condition. Encourage them to get tested so they can take steps to protect their health.

Read on to learn more about blood clots and hereditary antithrombin deficiency.
What is a blood clot?

- A blood clot is a clump of blood cells and proteins\(^1\)
- Blood clots form naturally to stop the bleeding when you have an injury (like a cut)\(^1\)

Platelets are a type of blood cell that is important for clotting.

- Sometimes, blood clots form inside blood vessels even when there isn’t an injury\(^2\)
- If large enough, these clots can stop blood flow and damage your organs\(^2\)

What are the symptoms of a blood clot?

- Abnormal blood clots may result in symptoms, such as:
  - Leg pain (calf or thigh)
  - Groin pain
  - Vision impairment
  - Lower leg swelling
  - Difficulty breathing
  - Weakness on one side of your body
People who get abnormal blood clots usually have one or more of these risk factors:

- Slow blood flow. For example:
  - Sitting for a long time
  - Cholesterol buildup in the blood vessels

- Smoking

- Certain medical conditions, including:
  - Other conditions, including obesity, liver disease, kidney disease and cancer, as well as taking certain medicines

- A genetic problem that affects the blood clotting process. These problems usually run in families. These conditions are often referred to as thrombophilias, or clotting disorders. People with these conditions have a lifelong risk of repeated blood clots.
One type of clotting disorder is hereditary antithrombin deficiency

- Antithrombin is one of the many substances in the body involved in preventing blood clots

**Anti = against**

**Thrombin = clotting**

People with hereditary antithrombin deficiency don’t make enough functional antithrombin. As a result, their blood is much more likely to clot

- More than 8 out of 10 patients with hereditary antithrombin deficiency have at least one clot by age 50

- About 6 in 10 patients with hereditary antithrombin deficiency have recurrent blood clots

= Have blood clot(s)

= Do not have blood clot(s)
How do I know if I have hereditary antithrombin deficiency?

• Your doctor may recommend a blood test for hereditary clotting disorders, including hereditary antithrombin deficiency, if:
  – You’ve already had a blood clot, particularly if the clot didn’t have an obvious cause or was unusual in some way
  – You have a family member with a history of blood clots

Why should I be tested for hereditary antithrombin deficiency?

• People with hereditary antithrombin deficiency who have already had at least one blood clot are at a higher risk for future clots

• If you know you have hereditary antithrombin deficiency, you and your doctor can take steps to lower your risk of a blood clot. These steps may include lifestyle changes and certain medicines
People with hereditary antithrombin deficiency are at especially high risk for blood clots in some situations, such as:

- Surgery
- Pregnancy and childbirth
- When they already have a blood clot

When are people with hereditary antithrombin deficiency at highest risk for blood clots?

- People with hereditary antithrombin deficiency are at especially high risk for blood clots in some situations, such as:

Should my family be tested for hereditary antithrombin deficiency?

- If you have hereditary antithrombin deficiency, other members of your family may have it, too.
- Encourage your family to talk with their doctors about getting tested for hereditary antithrombin deficiency.
How is hereditary antithrombin deficiency treated?

• Some people with hereditary antithrombin deficiency and a history of blood clots may need to take medicine every day to thin their blood and reduce the risk of blood clots³.

• However, most people with hereditary antithrombin deficiency will only need medicine in high-risk situations or when they have a clot. Medicine may include³,⁷:
  – Blood thinners (often warfarin or heparin)
  – Extra antithrombin (to replace the antithrombin missing from the body)

• Thrombate III® (antithrombin III [human]) replaces the antithrombin that is normally present in the body.⁵ It has been used by doctors for more than 20 years⁸.

• Studies have proven that Thrombate III effectively prevents blood clots in patients with hereditary antithrombin deficiency who are at high risk for developing a blood clot⁵.

• In clinical studies of Thrombate III, the most common side effects were dizziness, chest discomfort, nausea (upset stomach), and dysgeusia (foul taste in the mouth).
Thrombate III® (antithrombin III [human]) is indicated for the treatment of patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

In clinical studies with Thrombate III, the most common side effects were dizziness, chest discomfort, nausea, and dysgeusia.

The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Thrombate III is made from human plasma. Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk. No cases of transmission of viral disease or CJD have ever been identified for Thrombate III.

Please refer to the accompanying full Prescribing Information for complete prescribing details.
Take charge of your own health. Visit these websites to learn more about clotting disorders. Write down any questions you have, and take the list to your next doctor’s visit.

**National Blood Clot Alliance**  
[www.stoptheclot.org](http://www.stoptheclot.org)

**Foundation for Women & Girls with Blood Disorders**  
[www.fwgbd.org](http://www.fwgbd.org)

**The Coalition to Prevent Deep-Vein Thrombosis**  
[www.preventdvt.org](http://www.preventdvt.org)

**Vascular Disease Foundation**  
[www.thisisserious.org](http://www.thisisserious.org)

**Centers for Disease Control and Prevention**  

**ClotCare Online Resource**  
[www.clotcare.com](http://www.clotcare.com)

**Clot Connect**  
[www.clotconnect.org](http://www.clotconnect.org)

**Thrombate III® (antithrombin III [human])**  
[www.thrombate.com](http://www.thrombate.com)

With the exception of [www.thrombate.com](http://www.thrombate.com), these websites are third-party resources provided as a convenience to you. Grifols is not responsible for the content of these websites.
• Blood clots can stop blood flow and damage organs
• Some causes of blood clots, like hereditary antithrombin deficiency, run in families
• Your doctor may recommend a blood test for hereditary antithrombin deficiency if:
  – You’ve already had a blood clot
  – You have a family member with a history of blood clots
• Therapy for patients with hereditary antithrombin deficiency is available. It decreases the risk of blood clots during surgery and pregnancy/childbirth
• If you or a family member has suffered from a blood clot, have a conversation with your doctor about being tested for hereditary antithrombin deficiency
Have you or a family member had a blood clot?

Read this booklet to learn more about blood clots and hereditary antithrombin deficiency.

References:

Reimbursement Helpline
1-877-827-3462

For more information, visit www.thrombate.com.

Please see Important Safety Information on page 9 and refer to the accompanying full Prescribing Information for complete prescribing details.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
Antithrombin III (Human)

**THROMBATE III®**

**DESCRIPTION**

Antithrombin III (Human). THROMBATE III® is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III (ATIII). THROMBATE III is prepared from pooled units of human plasma from normal donors by modifications and refinements of the cold ethanol method of Cohn.(1) When reconstituted with Sterile Water for Injection, USP, THROMBATE III has a pH of 6.0–7.5, a sodium content of 110–210 mEq/l, a chloride content of 110–210 mEq/l, an albumin content of 0.075–0.125 mg/l, and a haptien content of not more than 0.1 IU heparin/IU ATIII. THROMBATE III contains no preservative and must be administered by the intravenous route.

Each vial of THROMBATE III contains the labeled amount of antithrombin III in international units (IU) per vial. The potency assignment has been determined with a standard calibrated against a World Health Organization (WHO) antithrombin III reference preparation.

The capacity of the THROMBATE III manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled-down process model using a wide range of viruses with diverse physicochemical properties. There are two dedicated virus inactivation/removal steps included in the THROMBATE III manufacturing process: a heat treatment step at 60°C ± 0.5°C for not less than 10 hours for virus inactivation and a nanofiltration step for effective removal of viruses as small as 18 nm.

The manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental transmissible spongiform encephalopathy (TSE) agent, considered as a model for the vCJD and CJD agents.(2–5)

An individual production step in the THROMBATE III manufacturing process has been shown to decrease TSE infectivity of that experimental model agent. The TSE reduction step is the Eutect I to Eutect II + III fractionation step (6.0 log10). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

**CLINICAL PHARMACOLOGY**

**Antithrombin III**, an alpha-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 0.7–0.8 mg/dl. It is the major plasma inhibitor of the serine proteases, thrombin (XIa), factor Xa, fibrinopeptide B, and factor XIIa, and XIIa, as well as plasmin.(8)

The neutralization rate of serine proteases by ATIII proceeds slowly in the absence of heparin, but is greatly accelerated in the presence of heparin.(8) ATIII is also an inhibitor of thrombin.(8) Inactivation of thrombin by ATIII occurs by formation of a covalent bond resulting in an inactive:1 stoichiometric complex between the two, involving an interaction of the active serine of thrombin and an arginine reactive site on ATIII.(8)

**ATIII in Plasma**

Plasma levels of ATIII are lower in neonates than adults, averaging approximately 60% in normal term infants.(24,25) ATIII levels in premature infants may be much lower.(24,25) Low plasma ATIII 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.(18)

**CONTRAINDICATIONS**

None known.

**WARNINGS**

Because THROMBATE III is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, bacteria, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for THROMBATE III. Inform patients that THROMBATE III is made from human plasma and may contain infectious agents that can cause disease. While the risk that THROMBATE III can contain an infectious agent has been reduced by screening plasma donors for prior exposure, testing donated plasma, and by inactivating or removing pathogens during manufacturing, patients should report any symptoms that concern them. All infections thought by a physician possibly to have been transmitted by this product should be reported to Grifols Therapeutics Inc. [1-800-520-2807].

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary ATIII deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

**PRECAUTIONS**

**General**

1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.

2. Administer only by the intravenous route.

3. THROMBATE III, once reconstituted, should be given alone, without mixing with other agents or diluting solutions.

4. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

**Drug Interactions**

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary ATIII deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

**Pregnancy Category B**

Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to THROMBATE III. It is not known whether THROMBATE III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Pediatric Use**

Safety and effectiveness in the pediatric population have not been established. The ATIII level in neonates of parents with hereditary ATIII deficiency should be measured immediately after delivery and within the first 24 hours of life. Neonatal thromboembolism, such as perinatal respiratory distress syndrome, is a concern in infants with congenital deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.(18)

**ADVERSE REACTIONS**

In clinical studies involving THROMBATE III, adverse reactions were reported in association with 17 of the 340 infusions during the clinical studies. Included were dizziness (8), chest pain (3), dyspnea (3), tachycardia (1), cherry red spot (1), chest pain (1), vision blurred (1), intestinal dilatation (1), urticaria (1), pyrexia (1), and wound secretion and hematomata (1). If adverse reactions are experienced, the infusion rate should be decreased, or if indicated, the infusion should be interrupted until symptoms abate.

**DOSEAGE AND ADMINISTRATION**

Each bottle of THROMBATE III has the functional activity, in international units (IU), stated on the label of the bottle. The potency assignment has been determined with a standard calibrated against a World Health Organization antithrombin III reference preparation.

Dosage should be determined on a individual basis based on the pre-therapy plasma ATIII level, in order to increase plasma ATIII levels to the level found in normal human plasma (80–120%). Dosage of THROMBATE III can be calculated from the following formula:

\[ \text{units required (IU)} = \frac{\text{Desired %} - \text{baseline % ATIII level}^* \times \text{body weight (kg)}}{1.4\%} \times \frac{\text{IU}}{\text{body weight (kg)}} \]

*Expressed as % normal level based on functional ATIII assay

The above formula is based on an expected incremental in vivo recovery above baseline levels for THROMBATE III of 1.4% per IU per kg administered.(14) Thus, if a 70 kg individual has a baseline ATIII level of 57%, in order to increase plasma ATIII to 80%, the initial THROMBATE III dose would be \( \left( \frac{120–57}{70} \times 1.4 \right) = 3150 \) IU total.
Vacuum Transfer

Antithrombin III (Human), THROMBATE III, is reconstituted with Sterile Water for Injection, USP. The dose and maintenance intervals should be individualized for each patient. When an infusion of THROMBATE III is indicated for a patient with hereditary deficiency to plasma ATIII levels achieved. In some situations, e.g., following surgery, (26) with hemorrhage or acute thrombosis, and during intravenous heparin therapy, recovery may vary, and initially levels should be drawn at baseline and 20 minutes after the start of the infusion. If the shrink band is absent or shows signs of wetting, the vial should be discarded.

**Rate of Administration**

The rate of administration should be adapted to the response of the individual patient, but administration of the entire dose in 10 to 20 minutes is generally well tolerated.

**HOW SUPPLIED**

THROMBATE III is supplied in a kit containing one single use vial of THROMBATE III lyophylized concentrate in sterile saline solution, one sterile filter needle, one sterile double-ended transfer needle, and one sterile filter needle. The total activity of ATIII in International Units is stated on the label of the THROMBATE III vial.

**STORAGE**

THROMBATE III should be stored at temperatures not to exceed 25°C (77°F). Freezing should be avoided as breakage of the diluent bottle might occur.

**CAUTION**

Rx only

U.S. federal law prohibits dispensing without prescription.

**REFERENCES**


**REVISED August 2013**

**NDC Number**

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<th>Carton (kit)</th>
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**GRIFFOLS**

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