Achieve Balance
Antithrombin (AT) and the coagulation cascade

80% of the natural anticoagulant effect against thrombin is dependent on AT\(^1,2\)

AT activity inhibits many clotting factors in the coagulation cascade\(^1-5\)

**Intrinsic Pathway**
AT inactivates factors IXa, XIa, and XIIa, interfering with the activation of factor X

**Extrinsic Pathway**
Tissue factor drives the initiation of coagulation and activation of factor X

**Factor Xa**
AT binds to factor Xa, inhibiting the conversion of prothrombin to its active form, thrombin

**Thrombin**
AT primarily binds to and inactivates thrombin, preventing it from acting on fibrinogen

**Fibrinogen ➔ Fibrin**
By inhibiting thrombin, AT disrupts the production of fibrin, the protein responsible for stable clot formation

1. Procoagulation factors bind to AT
2. Once bound to AT, procoagulation factors are cleared
3. The expansion of existing clots and formation of new clots are prevented

Please see Important Safety Information on back and refer to accompanying full Prescribing Information for THROMBATE III\(^{\circ}\) (antithrombin III [human]).
Achieve Balance
AT levels and heparin

The administration of heparin increases the anticlotting effects of AT 1000-fold\textsuperscript{1,2,6,7}

AT with heparin

The anticoagulation effects of heparin rely entirely on its interaction with AT\textsuperscript{6}

50\% to 85\% of patients with hereditary AT deficiency will have at least 1 thrombotic episode by age 50\textsuperscript{6,7}

\leq 80\% AT levels put patients at increased risk for thrombotic episodes\textsuperscript{8}

Patients who do not have the expected response to heparin may have hereditary AT deficiency\textsuperscript{9}

Important Safety Information

THROMBATE III\textsuperscript{®} (antithrombin III [human]) is indicated in patients with hereditary antithrombin deficiency for treatment and prevention of thromboembolism and for prevention of perioperative and peripartum thromboembolism.

Hypersensitivity reactions may occur. Should evidence of an acute hypersensitivity reaction be observed, promptly interrupt the infusion and begin appropriate treatment.

Because THROMBATE III is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. There is also the possibility that unknown infectious agents may be present in the product.

Perform coagulation tests to avoid excessive or insufficient anticoagulation and monitor for bleeding or thrombosis. Measure functional plasma AT levels with amidolytic or clotting assays; do not use immunoassays.

In clinical studies, the most common adverse reactions (\geq 5\% of subjects) were dizziness, chest discomfort, nausea, dysgeusia, and pain (cramps).

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT deficiency. Thus, in order to avoid bleeding, the dosage of heparin (or low molecular weight heparin) may need to be reduced during treatment with THROMBATE III.

Please see accompanying full Prescribing Information for THROMBATE III.

For intravenous use after reconstitution only
- Individualize dose to achieve AT level of 80% to 120% of normal human plasma. (2.1)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Target AT Level</th>
<th>Dose (Units)</th>
<th>Monitor AT Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading</td>
<td>120% of normal</td>
<td>120% - baseline % x body weight (kg) divided by 1.4%</td>
<td>baseline</td>
</tr>
<tr>
<td>Adjustment (as needed)</td>
<td>80% to 120% of normal</td>
<td>Target % - trough % x body weight (kg) divided by 1.4%</td>
<td>20 minutes (peak) post-injection</td>
</tr>
<tr>
<td>Maintenance (every 24 hours as needed)</td>
<td>80% to 120% of normal</td>
<td>Loading Dose x 0.6</td>
<td>approximately every 24 hours, as needed</td>
</tr>
</tbody>
</table>

Adapt the rate of administration to the response of the patient; typically the full dose is given over 10 to 20 minutes. (2.3)

### DOSAGE FORMS AND STRENGTHS

For injection: approximately 500 units, lyophilized powder in single-use vial for reconstitution. (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, discontinue THROMBATE III infusion and begin appropriate treatment. (5.1)
- Because THROMBATE III is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.2)
- Perform coagulation tests to avoid excessive or insufficient anticoagulation and monitor for bleeding or thrombosis. Measure functional plasma AT levels with amidolytic or clotting assays; do not use immunoassays. (5.3)

### ADVERSE REACTIONS

The most common adverse reactions (≥ 5% of subjects) in clinical studies were dizziness, chest discomfort, nausea, dysgeusia, and pain (cramps). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

### DRUG INTERACTIONS

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III. To avoid bleeding, reduce the dosage of heparin. (7)

### USE IN SPECIFIC POPULATIONS

Pregnancy: suspend heparin administration and continue THROMBATE III administration during labor and delivery. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.
table 2: adverse reactions occurring during hereditary deficiency trials

<table>
<thead>
<tr>
<th>Adverse Reaction*</th>
<th>Number of Subjects with Adverse Reaction (%)†</th>
<th>Number of Adverse Reactions (%) of All Infusions‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse reaction</td>
<td>9 (27)</td>
<td>29 (7.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (12)</td>
<td>8 (2.1)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>3 (9)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (9)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2 (6)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Pain (cramps)</td>
<td>2 (6)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Chills</td>
<td>1 (3)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Wound secretion and hematoma</td>
<td>1 (3)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>1 (3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Intestinal dilatation</td>
<td>1 (3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 (3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

* MedDRA Preferred Term; an adverse reaction is defined as any adverse event where either a) the event was related, or possibly related to the drug, b) the occurrence was during infusion or shortly after treatment, or c) the event recurred after withdrawal and re-administration (challenge/dechallenge).  
† N = 33 subjects  
‡ N = 389 infusions  
During clinical investigation of THROMBATE III, there were no reports of virus transmission. None of 12 subjects monitored for a median of 8 months (range 2–19 months) after receiving THROMBATE III became antibody positive to human immunodeficiency virus (HIV-1). None of 14 subjects monitored for ≥ 3 months demonstrated any evidence of hepatitis.

Drug Interactions  
The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT deficiency. Thus, in order to avoid bleeding, the dosage of heparin (or low molecular weight heparin) may need to be reduced during treatment with THROMBATE III.

Use in Specific Populations  

Pregnancy  

Risk Summary  
There are no data with THROMBATE III use in pregnant women to inform a drug-associated risk. However, there are clinical considerations [see Clinical Considerations]. It is not known whether THROMBATE III can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. THROMBATE III should be given to a pregnant woman only if clearly needed. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. 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.

Labor or Delivery  
Suspend heparin (or low molecular weight heparin) administration and continue THROMBATE III administration during labor and delivery.

Lactation  

Risk Summary  
There is no information regarding the presence of THROMBATE III in human milk, the effects on the breastfed infant, or the effects on milk production. The development of and health benefits of breastfeeding should be considered along with the mother’s clinical need for THROMBATE III and any potential adverse effects on the breastfed infant from THROMBATE III or from the underlying maternal condition.
11 DESCRIPTION

THROMBATE III, Antithrombin III (Human), is a sterile, non-pyrogenic concentrate of human antithrombin (AT) in lyophilized powder form for reconstitution for intravenous injection. When reconstituted with Sterile Water for Injection, USP, THROMBATE III has a pOH of 6.0 to 7.5 and contains 110 mEq/L to 210 mEq/L sodium, 110 mEq/L to 210 mEq/L chloride, 0.075 M to 0.125 M alanine, and not more than 0.1 unit of heparin per 1 unit of AT. THROMBATE III contains no preservative.

THROMBATE III is prepared from pooled units of human plasma from normal donors. 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 physiochemical 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 THROMBATE III manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD) and Creutzfeldt-Jakob disease (CJD) agents. 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 Effluent I + Effluent II + 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Antithrombin, an alpha 2-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 12.5 mg/dL and is the major plasma inhibitor of thrombin. Inactivation of thrombin by AT occurs by formation of a covalent bond resulting in an inactive 1:1 stoichiometric complex between the two, involving an interaction of the active serine of thrombin and an arginine reactive site on AT. AT is also capable of inactivating other components of the coagulation cascade including factors IXa, Xa, Xla, and XIIIa, as well as plasmin. The neutralization rate of serine proteases by AT proceeds slowly in the absence of heparin, but is greatly accelerated in the presence of heparin. As the therapeutic antithrombotic effect of heparin is mediated by AT, heparin in vivo is ineffective in the absence or near absence of AT.

After administration, THROMBATE III temporarily replaces the missing AT in patients with hereditary antithrombin deficiency.

12.3 Pharmacokinetics

In a clinical trial of THROMBATE III conducted in asymptomatic subjects with hereditary deficiency of AT, 8 subjects were administered a single dose of THROMBATE III at doses ranging from 25 units/kg to 125 units/kg. Pharmacokinetic parameters were determined using immunologic and functional AT assays (Table 3).

<table>
<thead>
<tr>
<th>AT Recovery, % /unit / kg</th>
<th>AT 50% Disappearance, hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6 ± 0.1*</td>
<td>17.4 ± 3.9</td>
</tr>
<tr>
<td>1.4 ± 0.1*</td>
<td>22.3 ± 8.6</td>
</tr>
</tbody>
</table>

* Mean ± SEM

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

THROMBATE III is supplied in a kit containing one single use vial of THROMBATE III lyophilized powder for reconstitution, one vial of Sterile Water for Injection, USP, one sterile double-ended transfer needle, and one sterile filter needle. The total activity of AT in International Units is stated on the label of the THROMBATE III vial.

Components used in the packaging of THROMBATE III are made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Inform patients that allergic-type hypersensitivity reactions are possible and instruct them to inform their physicians about any past or present known hypersensitivity to human plasma proteins prior to treatment with THROMBATE III. Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis and to notify their health care provider immediately if these events develop. [see Warnings and Precautions (5.1)]

Transmission of Infectious Disease

Inform patients that THROMBATE III is made from human plasma and may carry a risk of transmitting infectious agents that can cause disease (e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent). Inform patients that this risk has been reduced by screening plasma donors for prior exposure to certain infectious agents, by testing the donated plasma for markers of certain current infections, and by inactivating and/or removing pathogens during manufacturing. [see Warnings and Precautions (5.2)]