PRODUCT MONOGRAPH

THROMBATE III®

Antithrombin III (Human)

I.V. Injection, 500, IU

Manufacturer's Standard

Anticoagulant

Manufactured by:
Grifols Therapeutics Inc.
8368 US 70 Bus. Hwy West
Clayton, NC 27520

Distributed and Imported by:
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Mississauga, Ontario
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Submission Control No: 158117

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THROMBATE III®

Antithrombin III (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

Route of Administration	Dosage Form, Strength	Clinically Relevant Nonmedicinal Ingredients
intravenous	intravenous solution, 500IU	*For a complete listing see* DOSAGE FORMS, COMPOSITION AND PACKAGING *section.*

DESCRIPTION

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 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 alanine content of 0.075-0.125 M and a heparin content of NMT 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 labelled 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.

INDICATIONS AND CLINICAL USE

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 ATIII deficiency should be informed about the risk of thrombosis in connection with pregnancy and surgery and about the inheritance of the disease.

For information on the diagnosis of patients with hereditary antithrombin III deficiency, refer to WARNINGS AND PRECAUTIONS: Diagnosis.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or other anticoagulants or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.

WARNINGS AND PRECAUTIONS

General

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®.

THROMBATE III® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Canada Ltd. at 1-866-482-5226. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient.

Administration and Handling

Administer only by the intravenous route.

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

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

Diagnosis

The diagnosis of hereditary antithrombin III deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma ATIII levels, and the exclusion of acquired deficiency.

ATIII 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 ATIII deficiencies (2).

The ATIII level in neonates of parents with hereditary ATIII deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported) (3).

Plasma levels of ATIII are lower in neonates than adults, averaging approximately 60% in normal term infants (4,5). ATIII levels in premature infants may be much lower (4,5). 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 (6).

Special Populations

Pregnant Women

Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of 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.

Nursing Women

Because of the potential for unknown effects from THROMBATE III® in infants being nursed by mothers taking THROMBATE III®, a decision should be made to either discontinue nursing or discontinue the administration of THROMBATE III®, taking into account the importance of THROMBATE III® therapy to the mother and the possible risk to the infant.

Pediatrics (< 18 years of age)

Only a few neonates and children have so far been treated with THROMBATE III®. Safety and effectiveness in children have not been established.

For diagnosis in neonates, see WARNINGS AND PRECAUTIONS: Diagnosis.

Monitoring and Laboratory Tests

It is recommended that ATIII plasma levels be monitored during the treatment period. Functional levels of ATIII in plasma may be measured by amidolytic assays using chromogenic substrates or by clotting assays.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

If adverse reactions are experienced, the infusion rate should be decreased, or if indicated, the infusion should be interrupted until symptoms abate.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In clinical studies involving THROMBATE III®, adverse reactions have been reported in association with 17 of 340 infusions (5.0%). The most common reported adverse reactions are presented in Table 2.

Table 2 – Clinical Trial Adverse Drug Reactions

	THROMBATE III® (n=340)
Eye Disorders	
Filmy vision	1 (0.3%)
Gastrointestinal Disorders	
Dysgeusia	3 (0.9%)
Gastrointestinal fullness	1 (0.3%)
Nausea	3 (0.9%)
General Disorders and Administration Site Conditions	
Chest pain	1 (0.3%)
Chest tightness	3 (0.9%)
Chills	2 (0.6%)
Pyrexia	1 (0.3%)
Immune System Disorders	
Urticaria	1 (0.3%)

Table 2 – Clinical Trial Adverse Drug Reactions

	THROMBATE III® (n=340)
Musculoskeletal and Connective Tissue Disorders	
Cramps	2 (0.6%)
Nervous System Disorders	
Dizziness	8 (2.4%)
Respiratory, Thoracic and Mediastinal Disorders	
Shortness of Breath	1 (0.3%)
Vascular Disorders	
Haematoma	1 (0.3%)

Post-Market Adverse Drug Reactions

The following rare adverse events have been reported during post-marketing use of THROMBATE III®.

Possibly drug related:	hemolytic anemia
	Hypocalcemia
Unlikely drug related:	cerebral hemorrhage
	gastrointestinal hemorrhage
	cardiac arrest
Not drug related:	cerebral hemorrhage
	cardiac arrest due to multiple organ failure
	renal failure

DRUG INTERACTIONS

Drug-Drug Interactions

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

Table 3 – Established or Potential Drug-drug Interactions

Proper Name	Ref	Effect	Clinical Comment
heparin	T	The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III®.	In order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III®.

Legend: C=Case Study; CT=Clinical Trial; T=Theoretical

Drug-Food Interactions

No interactions are known.

Drug-Herb Interactions

No interactions are known.

Drug-Laboratory Interactions

No interactions are known.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The recommendations for dosing are provided as a general guideline for therapy only. The exact loading and maintenance dosages and dosing intervals should be individualized for each subject, based on the individual clinical conditions, response to therapy, and actual plasma ATIII levels achieved. In some situations, e.g., following surgery (7,8), with haemorrhage or acute thrombosis (9,10) and during intravenous heparin administration (8,11,12), in vivo survival of infused THROMBATE III® has been reported to be shortened, resulting in the need to administer THROMBATE III® more frequently.

Recommended Dose and Dosage Adjustment

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 an individual basis based on the pre-therapy plasma antithrombin III (ATIII) level, in order to increase plasma ATIII levels to the level found in normal human plasma (100%). Dosage of THROMBATE III® can be calculated from the formula represented by Equation 1.

Equation 1 – Calculation of THROMBATE III® Dosage

$$\text{units required (IU)} = \frac{[(\text{desired ATIII level}) - (\text{baseline ATIII level})^{a}] \times \text{weight (kg)}}{1.4}$$

a 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. Thus, if a 70 kg individual has a baseline ATIII level of 57%, in order to increase plasma ATIII to 120%, the initial THROMBATE III® dose would be [(120-57) x 70]/1.4 = 3150 IU total.

However, recovery may vary, and initially levels should be drawn at baseline and 20 minutes post infusion. Subsequent doses can be calculated based on the recovery of the first dose. These recommendations are intended only as a guide for therapy. The exact loading dose and maintenance intervals should be individualized for each patient.

It is recommended that following an initial dose THROMBATE III®, plasma levels of ATIII be initially monitored at least every 12 hours and before the next infusion of THROMBATE III® to

maintain plasma ATIII levels greater than 80%. In some situations, e.g., following surgery (10), haemorrhage or acute thrombosis (9,10), and during intravenous heparin administration (8,11,12), the half-life of Antithrombin III (Human) has been reported to be shortened, and in such conditions, plasma ATIII levels should be monitored more frequently, administering THROMBATE III® as necessary.

When an infusion of THROMBATE III® is indicated for a patient with hereditary deficiency to control an acute thrombotic episode or prevent thrombosis following surgical or obstetrical procedures, it is desirable to raise the ATIII level to normal and maintain this level for 2 to 8 days, depending on the indication for treatment, type and extent of surgery, patient's medical condition, past history and physician's judgment. Concomitant administration of heparin in each of these situations should be based on the medical judgement of the physician.

As a general recommendation, the following therapeutic program may be utilized as a starting program for treatment, modifying the program based on the actual plasma ATIII levels achieved:

a) An initial loading dose of THROMBATE III® calculated to elevate the plasma ATIII level to 120%, assuming an expected rise over the baseline plasma ATIII level of 1.4% (functional activity) per IU per kg of THROMBATE III® administered. Thus, if an individual has a baseline ATIII level of 57%, the initial THROMBATE III® dose would be (120-57)/1.4 = 45 IU/kg.

b) Measure pre- and 20 minutes post-infusion (peak) plasma antithrombin III levels following the initial loading dose, plasma antithrombin III level after 12 hours, then preceding the next infusion (trough level). Subsequently measure antithrombin 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 ATIII levels achieved.

Administration

THROMBATE III® must be administered intravenously.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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

Reconstitution

THROMBATE III® is reconstituted with Sterile Water for Injection, USP at room temperature prior to administration. THROMBATE III® should be filtered through a sterile filter needle as

supplied in the package prior to use, and should be administered within 3 hours following reconstitution. THROMBATE III® may be infused over 10-20 minutes.

Table 4 – Reconstitution of THROMBATE III®

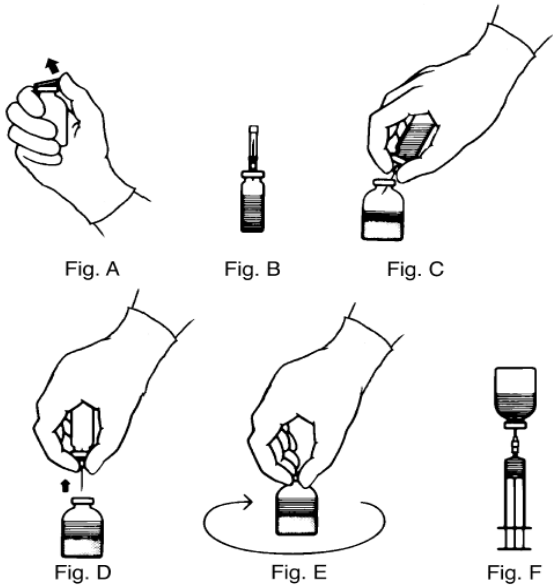
Product Code	Approximate ATIII Potency	Volume of Diluent to be Added to Vial
603-20	500 IU	10 mL

Vacuum Transfer

1. Thrombate III® and diluent should be at room temperature before reconstitution
2. Remove shrink band from THROMBATE III® vial. **If the shrink band is absent or shows signs of tampering, do not use the product and notify Grifols Canada Ltd immediately.**
3. Remove the plastic flip tops from each vial (Figure 1: A). Cleanse vial tops (grey stoppers) with alcohol swab and allow surface to dry. After cleaning, do not allow anything to touch the stopper.
4. Carefully remove the sheath from the short end of the transfer needle. Insert the exposed needle into the diluent vial to the hub. (Figure 1: B).
5. Carefully grip the sheath of the other end of the transfer needle and twist to remove it.
6. Invert the diluent vial and insert the attached needle into the concentrate vial at a 45°angle (Figure 1: C). This will direct the stream of diluent against the wall of the concentrate vial and minimize foaming. The vacuum will draw the diluent into the concentrate vial.*
7. When diluent transfer is complete, remove the diluent vial and transfer needle (Figure 1: D).
8. Immediately after adding the diluent, swirl continuously until completely dissolved (Figure 1: E). Some foaming may occur, but attempt to avoid excessive foaming. The vial should then be visually inspected for particulate matter and discoloration prior to administration.
9. Clean the top of the vial of reconstituted THROMBATE III® again with alcohol swab and let surface dry.
10. Attach the filter needle (from the package) to sterile syringe. Withdraw the THROMBATE III® solution into the syringe through the filter needle (Figure 1: F).
11. Remove the filter needle from the syringe and replace with an appropriate injection or butterfly needle for administration. Discard filter needle into a puncture-proof container.
12. If the same patient is using more than one vial of THROMBATE III®, the contents of multiple vials may be drawn into the same syringe through the filter needles provided.

*If vacuum is lost in the concentrate vial, use a sterile syringe to remove the sterile water from the diluent vial and inject it into the concentrate vial, directing the stream of fluid against the wall of the vial.

Figure 1 – Steps in the Reconstitution of THROMBATE III®



ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The prevalence of the hereditary deficiency of ATIII is estimated to be one per 2000 to 5000 in the general population (13,14). The pattern of inheritance is autosomal dominant. In affected individuals, spontaneous episodes of thrombosis and pulmonary embolism may be associated with ATIII levels of 40-60% of normal (14). These episodes usually appear after the age of twenty, the risk increasing with age and in association with surgery, pregnancy and delivery. The frequency of thromboembolic events in hereditary antithrombin III (ATIII) deficiency during pregnancy has been reported to be 70% and several studies of the beneficial use of Antithrombin III (Human) concentrates during pregnancy in women with hereditary deficiency have been reported (6,15,16). In many cases, however, no precipitating factor can be identified for venous thrombosis or pulmonary embolism (14). Greater than 85% of individuals with hereditary ATIII deficiency have had at least one thrombotic episode by the age of 50 years (14). In about 60% of patients thrombosis is recurrent. Clinical signs of pulmonary embolism occur in 40% of affected individuals (14). In some individuals, treatment with oral anticoagulants leads to an increase in the endogenous levels of ATIII, and treatment with oral anticoagulants may be effective in the prevention of thrombosis in such individuals (14,17).

Antithrombin III (ATIII), an $alpha_2$-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 12.5 mg/dL (18,19) and is the major plasma inhibitor of thrombin (13). Inactivation of thrombin by ATIII 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 ATIII (13). ATIII is

also capable of inactivating other components of the coagulation cascade including Factors IXa, Xa, XIa, and XIIa, as well as plasmin (13).

The neutralization rate of serine proteases by ATIII proceeds slowly in the absence of heparin, but is greatly accelerated in the presence of heparin (13). As the therapeutic antithrombotic effect in vivo of heparin is mediated by ATIII, heparin is ineffective in the absence or near absence of ATIII (13,14,17,20,21).

In clinical studies, patients with hereditary ATIII deficiency and histories of thromboembolism were treated prophylactically with THROMBATE III®. None of these patients developed a thrombotic complication. In addition, treatment with THROMBATE III® reversed heparin resistance in two patients with hereditary ATIII deficiency being treated for thrombosis or thromboembolism. For further details, refer to Product Monograph PART II: CLINICAL TRIALS.

Pharmacodynamics

See ACTION AND CLINICAL PHARMACOLOGY: Mechanism of Action.

Pharmacokinetics

In clinical studies of THROMBATE III®, conducted in 10 asymptomatic subjects with hereditary deficiency of ATIII, the mean in vivo recovery of ATIII was 1.6% per unit per kg administered based on immunologic ATIII assays, and 1.4% per unit per kg administered based on functional ATIII assays (22). The mean 50% disappearance time (the time to fall to 50% of the peak plasma level following an initial administration) was approximately 22 hours and the biologic half-life was 2.5 days based on immunologic assays and 3.8 days based on functional assays of ATIII. These values are similar to the half-life for radiolabeled antithrombin III (Human) reported in the literature of 2.8-4.8 days (7,9,23).

Duration of Effect

See ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics.

STORAGE AND STABILITY

THROMBATE III® should be stored at a temperature not to exceed 25°C. Freezing should be avoided as breakage of the diluent bottle might occur.

DOSAGE FORMS, COMPOSITION AND PACKAGING

THROMBATE III® is supplied in single dose vials with the potency in international units (500 IU) stated on the label of each vial. A suitable volume (10 mL) of Sterile Water for Injection, USP, a sterile double ended transfer needle and a sterile filter needle are provided.

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 alanine content of 0.075-0.125 M and a heparin content of NMT 0.1 IU heparin/IU ATIII.

THROMBATE III® contains no preservative.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	THROMBATE III®
Chemical name:	Antithrombin III (ATIII)
Molecular weight:	58,000 D

Product Characteristics

THROMBATE III® is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III (ATIII).

Viral Inactivation

The removal and inactivation of spiked model enveloped and non-enveloped viruses during the manufacturing process for THROMBATE III® has been validated in laboratory studies. Human immunodeficiency virus, type 1 (HIV-1), was chosen as the relevant virus for blood products; bovine viral diarrhea virus (BVDV) was chosen to model hepatitis C virus; and pseudorabies virus (PRV) was chosen to model hepatitis B virus and the herpes viruses. Hepatitis A virus (HAV) and reovirus type 3 were chosen as relevant non-enveloped viruses for blood products with resistance to physical and chemical inactivation. In addition, porcine parvovirus (PPV) was chosen to model human parvovirus B19.

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.

CLINICAL TRIALS

In clinical studies of THROMBATE III®, none of 13 patients with hereditary ATIII deficiency and histories of thromboembolism treated prophylactically on 16 separate occasions with THROMBATE III® for high thrombotic risk situations (11 surgical procedures, 5 deliveries) developed a thrombotic complication. Heparin was also administered in 3 of the 11 surgical procedures. Eight patients with hereditary ATIII deficiency were treated with THROMBATE III® as well as heparin for major thrombotic or thromboembolic complications, with 7 patients recovering. Treatment with THROMBATE III® reversed heparin resistance in two patients with hereditary ATIII deficiency being treated for thrombosis or thromboembolism.

During clinical investigation of THROMBATE III®, 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 B, or hepatitis C.

DETAILED PHARMACOLOGY

Animal Pharmacology

Antithrombin III (Human) concentrates were examined for their clearance kinetics in rabbits. The mean biologic half-life of ATIII (Human) was compared to that of a highly purified, non-heat treated rabbit ATIII. Both preparations had similar clearance kinetics in both the distribution and catabolic phases. The circulating half-life of ATIII (Human) in rabbits was comparable to non-heat treated rabbit ATIII itself.

Human Pharmacology

In clinical studies of THROMBATE III®, conducted in 10 asymptomatic subjects with hereditary deficiency of ATIII, the mean in vivo recovery of ATIII was 1.6% per unit per kg (based on immunologic ATIII assays), and 1.4% per unit per kg administered (based on functional ATIII assays) (22). The mean 50% disappearance time was approximately 22 hours and the biologic half-life was 2.5 days based on immunological assays and 3.8 days based on functional assays of ATIII (22).

TOXICOLOGY

Acute Toxicity

The acute intravenous toxicity of Antithrombin III (Human) was determined in mice, rats and rabbits. The intravenous LD_{50}'s were >156 mL/kg, >125 mL/kg and >21.6 mL/kg, respectively. Repeated administration studies were performed in rabbits. The animals were administered ATIII (Human) intravenously, at a dose of 9.6 mL/kg for five successive days. The concentration of ATIII (Human) used in these studies was 55.4 IU/mL. No adverse effects were seen in rabbits with regard to body weight gain, hematology or blood chemistry. Histopathological examination of tissues showed absence of any adverse effects related to ATIII administration.

Reproductive Toxicology

Reproduction studies have been performed in rats and rabbits at doses up to 320 IU/kg and have revealed no evidence of harm to the fetus due to Antithrombin III (Human). In rabbits, the no observable effect level is considered to be 2.6 mL/kg/day (160 IU/kg) for maternal toxicity and 5.2 mL/kg/day (320 IU/kg) for developmental toxicity.

REFERENCES

1. Cohn EJ, Srong LE, Hughes WLJ, Mulford DJ, Ashworth JN, Melin M, et al. Preparation and properties of serum and plasma proteins: IV. A system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. J Am Chem Soc 1946;68(3):459-75.

2. Sas G, Blasko G, Banhegyi D, Jako J, Palos LA. Abnormal antithrombin III (antithrombin III "Budapest") as a cause of a familial thrombophilia. Thromb Diath Haemorrh 1974;32(1):105-15.

3. Bjarke B, Herin P, Blomback M. Neonatal aortic thrombosis. A possible clinical manifestation of congenital antithrombin 3 deficiency. Acta Paediatr Scand 1974;63(2):297-301.

4. Hathaway WE. Perinatal coagulation (monographs in neonatology). New York: Grune & Stratton; 1978.

5. Peters M, Jansen E, ten Cate JW, Kahle LH, Ockelford P, Breederveld C. Neonatal antithrombin III. Br J Haematol 1984;58(4):579-87.

6. Hellgren M, Tengborn L, Abildgaard U. Pregnancy in women with congenital antithrombin III deficiency: experience of treatment with heparin and antithrombin. Gynecol Obstet Invest 1982;14(2):127-41.

7. Knot EA, de Jong E, ten Cate JW, Iburg AH, Henny CP, Bruin T, et al. Purified radiolabeled antithrombin III metabolism in three families with hereditary AT III deficiency: application of a three-compartment model. Blood 1986;67(1):93-8.

8. Marciniak E, Gockerman JP. Heparin-induced decrease in circulating antithrombin-III. Lancet 1977;2(8038):581-4.

9. Collen D, Schetz J, de Cock F, Holmer E, Verstraete M. Metabolism of antithrombin III (heparin cofactor) in man: effects of venous thrombosis and of heparin administration. Eur J Clin Invest 1977;7(1):27-35.

10. Mannucci PM, Boyer C, Wolf M, Tripodi A, Larrieu MJ. Treatment of congenital antithrombin III deficiency with concentrates. Br J Haematol 1982;50(3):531-5.

11. Kakkar VV, Bentley PG, Scully MF, MacGregor IR, Jones NA, Webb PJ. Antithrombin III and heparin. Lancet 1980;1(8159):103-4.

12. O'Brien JR, Etherington MD. Effect of heparin and warfarin on antithrombin III. Lancet 1977;2(8050):1231.

13. Rosenberg RD. Actions and interactions of antithrombin and heparin. N Engl J Med 1975;292(3):146-51.

14. Thaler E, Lechner K. Antithrombin III deficiency and thromboembolism. Clin Haematol 1981;10(2):369-90.

15. Brandt P. Observations during the treatment of antithrombin-III deficient women with heparin and antithrombin concentrate during pregnancy, parturition, and abortion. Thromb Res 1981;22(1-2):15-24.

16. Samson D, Stirling Y, Woolf L, Howarth D, Seghatchian MJ, de Chazal R. Management of planned pregnancy in a patient with congenital antithrombin III deficiency. Br J Haematol 1984;56(2):243-9.

17. Marciniak E, Farley CH, DeSimone PA. Familial thrombosis due to antithrombin 3 deficiency. Blood 1974;43(2):219-31.

18. Murano G, Williams L, Miller-Andersson M, Aronson DL, King C. Some properties of antithrombin-III and its concentration in human plasma. Thromb Res 1980;18(1-2):259-62.

19. Rosenberg RD, Bauer KA, Marcum JA. Antithrombin III, the heparin-antithrombin system. In: Murano G, editor. Reviews of hematology. Westbury, NY: PJD Publications; 1986. pp. 351-416.

20. Blauhut B, Necek S, Kramar H, Vinazzer H, Bergmann H. Activity of antithrombin III and effect of heparin on coagulation in shock. Thromb Res 1980;19(6):775-82.

21. Winter JH, Fenech A, Ridley W, Bennett B, Cumming AM, Mackie M, et al. Familial antithrombin III deficiency. Q J Med 1982;51(204):373-95.

22. Schwartz RS, Bauer KA, Rosenberg RD, Kavanaugh EJ, Davies DC, Bogdanoff DA. Clinical experience with antithrombin III concentrate in treatment of congenital and acquired deficiency of antithrombin. The Antithrombin III Study Group. Am J Med 1989;87(3B):53S-60S.

23. Tengborn L, Frohm B, Nilsson LE, Nilsson IM. Antithrombin III concentrate: its catabolism in health and in antithrombin III deficiency. Scand J Clin Lab Invest 1981;41(5):469-77.

PART III: CONSUMER INFORMATION

THROMBATE III®

Antithrombin III (Human)

This leaflet is Part 3 of a three-part "Product Monograph" published when THROMBATE III® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about THROMBATE III®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Hereditary antithrombin III deficiency is a genetic disease which leads to low levels of antithrombin III protein in the blood. Without enough antithrombin III in the blood, abnormal blood clots may form, which may damage organs.

THROMBATE III® is used for patients with hereditary antithrombin III deficiency when they have surgery, are pregnant or in labour, or have a blood clot.

What it does:

THROMBATE III® replaces some of the antithrombin III protein missing from patients with hereditary antithrombin III deficiency.

When it should not be used:

You should not be given THROMBATE III® if you have had an allergic reaction to a previous antithrombin III injection, or to any of the other ingredients in the medicine.

What the medicinal ingredient is:

THROMBATE III® contains human antithrombin III protein.

What the nonmedicinal ingredients are:

THROMBATE III® also contains sodium, chloride, the amino acid alanine, and heparin. It does not contain any preservative.

What dosage forms it comes in:

THROMBATE III® comes in 500 IU single dose vials.

THROMBATE III® like other products made from human plasma, part of our blood, may contain viruses or other agents that can cause infection and illness. However, the processes used to make THROMBATE III® are specifically designed with the ability to destroy or remove these agents if they are present. You should discuss the risks and benefits of this product with your healthcare provider.

BEFORE you use THROMBATE III® talk to your doctor or pharmacist if:

- you are pregnant or breastfeeding
- you have had an allergic reaction to antithrombin III or any of the other ingredients in the medicine

INTERACTIONS WITH THIS MEDICATION

THROMBATE III® increases the effects of heparin. Talk with your healthcare professional if you are currently receiving heparin.

See also ABOUT THIS MEDICATION: When it should not be used, and SIDE EFFECTS AND WHAT TO DO ABOUT THEM.

PROPER USE OF THIS MEDICATION

Usual dose

The exact amount and timing of doses varies for each patient. Your doctor will determine the amount of THROMBATE III® that is right for you and when your treatments are to be scheduled. A doctor, nurse or other caregiver trained to give injections will give your treatment.

Missed Dose

It is important that you receive THROMBATE III® as instructed by your healthcare professional. If your doctor tells you that more than one treatment is required, you should consult him/her if a treatment appointment is missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

In clinical studies with patients using THROMBATE III®, the most common side effects were abdominal cramps, bowel fullness, bruising and swelling, chest pain, chest tightness, chills, dizziness, fever, film over eye(s), foul taste, hives, shortness of breath, light-headedness, and nausea.

Contact your doctor immediately if, while undergoing THROMBATE III® treatment or following treatment, you experience any of these side effects:

- chills or fever
- chest tightness
- chest pain
- hives
- shortness of breath
- severe abdominal cramps
- severe dizziness or light-headedness
- severe nausea

This is not a complete list of side effects. For any unexpected effects while taking THROMBATE III®, contact your doctor or pharmacist.

HOW TO STORE IT

THROMBATE III® should be stored at temperatures not to exceed 25°C. It should not be frozen or used past the expiration date.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance :

By toll-free telephone:	866-234-2345
By toll-free fax:	866-678-6789
Online	www.healthcanada.gc.ca/medeffect
By email:	CanadaVigilance@hc-sc.gc.ca
By regular mail:	Canada Vigilance National Office Marketed Health Products Safety and Effectiveness Information Bureau Marketed Health Products Directorate Tunney's Pasture, AL 0701C Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the distributor, Grifols Canada Ltd., at: 1-866-482-5226

This leaflet was prepared by:

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