HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVITHROM safely and effectively. See full prescribing information.

EVITHROM* Thrombin, Topical (Human)
For Topical Use Only
Initial U.S approval: 2007

INDICATIONS AND USAGE

- As an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques is ineffective or impractical (1).
- May be used in conjunction with an Absorbable Gelatin Sponge, USP (1).

DOSAGE AND ADMINISTRATION

- **For topical use only. DO NOT INJECT (2.2).**
- The amount required depends upon the area of tissue to be treated and the method of application. In clinical studies, volumes up to 10 ml were used in conjunction with Absorbable Gelatin Sponge, USP (2.2).
- Thaw prior to use (2.1). The time between thawing and application is restricted (16).
- Vials are for single use only. Discard unused contents (2.2).

DOSAGE FORMS AND STRENGTHS

- Vials of 2 ml, 5 ml, or 20 ml frozen solution containing 800-1200 IU/ml of Thrombin, Topical (Human) (3).

CONTRAINDICATIONS

- **Do not inject directly into the circulatory system (4).**
- **Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products (4).**
- **Do not use for the treatment of severe or brisk arterial bleeding (4).**

WARNINGS AND PRECAUTIONS

- May carry a risk of transmitting infectious agents such as viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite manufacturing steps designed to reduce the risk of viral transmission (11).
- **Potential risk of thrombosis if absorbed systemically (5.2, 11).**

ADVERSE REACTIONS

- Anaphylactic reactions may occur (6).
- Adverse events were reported in the clinical trial with similar frequency in the two study groups (EVITHROM or bovine thrombin group). The most common adverse event reported was procedural complications and pruritus (6). None of the adverse events reported was considered causally related to EVITHROM administration.
- Immunogenicity was evaluated by testing for the development of antibodies to highly purified antigens: human thrombin, human Factor V/Va, bovine thrombin and bovine Factor V/Va. None of the patients treated with EVITHROM developed antibodies to human thrombin or to human Factor V/Va.

To report SUSPECTED ADVERSE REACTIONS, contact ETHICON Customer Support Center at (877) 384-4266 **or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.

USE IN SPECIFIC POPULATIONS

- Geriatrics: No differences in safety or effectiveness were observed between the elderly and younger patients. Greater susceptibility of older patients to adverse reactions cannot be ruled out (8.5).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2007

FULL PRESCRIBING INFORMATION: CONTENTS[1]

1 *Sections or subsections omitted from the full prescribing information are not listed*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EVITHROM Thrombin, Topical (Human) is indicated an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques is ineffective or impractical.

EVITHROM Thrombin, Topical (Human) may be used in conjunction with an Absorbable Gelatin Sponge, USP.

2 DOSAGE AND ADMINISTRATION

2.1 Thawing prior to application

Thaw EVITHROM in one of the following ways:

- 2°C to 8°C (refrigerator): Vials thaw within 1 day.
- 20°C to 25°C (room temperature): Vials thaw within 1 hour.
- 37°C **for 2 ml and 5 ml vials only**: Vials thaw within 10 minutes and must not be left at this temperature for longer than 10 minutes. The temperature must not exceed 37°C.

Remove the flip-off plastic cap from the vial to expose the rubber stopper. Using a sterile needle and syringe, you may withdraw the thrombin solution from the glass vial. Alternatively, you can remove the rubber stopper (by removing the metal pull tab) to transfer EVITHROM into a sterile container using aseptic techniques.

The time limitations between thawing and application are described in the HOW SUPPLIED/STORAGE AND HANDLING (16).

2.2 Application techniques

EVITHROM is used topically and should be applied on the surface of bleeding tissue only. DO NOT INJECT.

EVITHROM alone

1. Sponge target surface (don't wipe) or suction free of blood before application.
2. The surface may be flooded with EVITHROM using a sterile syringe and small gauge needle.
3. After treatment, avoid sponging the clot to assure that it remains securely in place.

EVITHROM in conjunction with Absorbable Gelatin Sponge, USP

1. Transfer EVITHROM into a sterile container using aseptic techniques.
2. Immerse gelatin sponge of desired shape in the EVITHROM solution.
3. Vigorously knead the sponge with moistened gloved fingers until all air is expelled and it can return to its original size and shape.
4. Hold the saturated sponge in place with gauze or cotton pledget using moderate pressure until hemostasis is achieved.

The amount of EVITHROM required depends upon the area of tissue to be treated and the method of application. As an approximate guide, volumes up to 10 ml were used in clinical studies where EVITHROM was used in conjunction with Absorbable Gelatin Sponge, USP.

Vials are for single use only. Discard unused contents.

3 DOSAGE FORMS AND STRENGTHS

EVITHROM is supplied as a frozen solution in the following packages:

- Vial containing 2 ml, 5 ml or 20 ml. Each vial contains 800-1200 IU/ml of Thrombin, Topical (Human).

4 CONTRAINDICATIONS

- **Do not inject directly into the circulatory system.**
- **Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products.**
- **Do not use for the treatment of severe or brisk arterial bleeding.**

5 WARNINGS AND PRECAUTIONS

5.1 Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmitting 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 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.

All infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to ETHICON Customer Support Center at (877) 384-4266. The physician should discuss the risks and benefits of this product with the patient.

5.2 Potential risk of thrombosis if absorbed systemically

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Anaphylactic reactions may occur in rare cases. No adverse events of this type were reported during the conduct of the clinical trials. Mild reactions can be managed with anti-histamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

6.1 Clinical trials experience

In a phase III study of 305 subjects where EVITHROM (n=153) was compared with bovine thrombin (n=152), occurrence of adverse events was not statistically different between the two groups.

Overall, adverse events occurred in similar proportions of subjects in the two study groups. The most common adverse event reported was procedural complications and pruritus (6). No clinically significant differences were seen in age (<65 years, >65 years) or gender subgroup analyses of adverse events.

At least one serious adverse event (SAE) was reported for 26/153 (17%) subjects treated with human thrombin and 17/152 (11%) subjects treated with bovine thrombin. The SAEs reported were associated with post-surgical complications (e.g. wound infection 3/153 for EVITHROM and 2/152 for bovine thrombin) and the medical condition of the subject and were not considered related to study drug. Two subjects (1.3%) in EVITHROM group experienced a treatment emergent severe adverse event: respiratory arrest and post-procedural hematoma (in one subject) and extradural hematoma. Three subjects in the bovine thrombin group experienced a treatment emergent severe adverse event: hyperhidrosis, pyrexia and post-procedural hematoma. None of the adverse events reported was considered causally related to EVITHROM administration.

No deaths were reported during the study period.

Viral serology was not monitored during the study with EVITHROM. However, no adverse events indicative of infection with transfusion-transmissible agents were reported.

Table 1: Incidence of Subjects with related adverse events reported in at least 2% of subjects treated with either human or bovine thrombin

	Thrombin		
System Organ Class/Adverse Event	**EVITHROM (n=153)**	**Bovine (n=152)**	**Total (n=305)**
Investigations	**11 (7.2%)**	**14 (9.2%)**	**25 (8.2%)**
Activated partial thromboplastin time increased	4 (2.6%)	8 (5.3%)	12 (3.9%)
International normalized ratio increased	4 (2.6%)	5 (3.3%)	9 (3.0%)
Lymphocyte count decreased	4 (2.6%)	2 (1.3%)	6 (2.0%)
Prothrombin time prolonged	4 (2.6%)	8 (5.3%)	12 (3.9%)
Neutrophil count increased	3 (2.0%)	2 (1.3%)	5 (1.6%)
Skin and Subcutaneous Tissue Disorders	**1 (0.7%)**	**3 (2.0%)**	**4 (1.3%)**
Pruritis	1 (0.7%)	3 (2.0%)	4 (1.3%)
General Disorders and Administration Site Conditions	**0**	**3 (2.0%)**	**3 (1.0%)**

Immunogenicity

In the clinical study, serum samples were collected at baseline and at 5 weeks post-surgery for evaluation of antibodies to bovine Thrombin, bovine Factor V/Va, human Thrombin, and human Factor V/Va. Samples were collected at both time points for 81.3% of the subjects. The ELISA data were adjudicated by a panel of experts blinded to treatment assignment. After reviewing all data, the panel used an algorithm for assigning outcomes for each antigen: seroconversion negative or seroconversion positive.

The protocol did not specify any comparative analysis for immunogenicity data, only descriptive statistics. The adjudicated results show that 3.3% of the subjects treated with EVITHROM developed antibodies to any of the four antigens, compared to 12.7% of the subjects developing antibodies in the control group (bovine Thrombin).

7.94% of the subjects treated with bovine Thrombin (control group) developed antibodies to bovine thrombin and 9.52% of these subjects developed antibodies to bovine Factor V/Va. A few control subjects had antibodies that cross-reacted with human thrombin, but none had antibodies that cross-reacted with human Factor V/Va.

None of the patients treated with EVITHROM developed detectable antibodies to human thrombin or to human Factor V/Va.

The detection of antibody formation is highly dependent upon the sensitivity and specificity of the assay. The observed incidence of a positive signal in an assay may be influenced by several factors including timing of sampling, sample handling, concomitant medications, or underlying disease. Therefore, direct comparison of

incidence of antibody development to human or bovine thrombin or Factor V/Va following administration of EVITHROM with incidence of antibody development following administration of other products may be misleading and the clinical significance of these findings is unknown.

7 DRUG INTERACTIONS

No drug interactions are known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category C

Adequate and well-controlled studies in pregnant women have not been performed. EVITHROM should be used in pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus. Studies to evaluate the potential reproductive/developmental toxicity of EVITHROM have not been performed due to the human origin of thrombin. However, studies to evaluate the potential reproductive/developmental toxicity of residual levels of Triton X-100 and tri-n-butyl phosphate (solvent/detergent reagents) were conducted in animals and are summarized in the Non Clinical Toxicology section (13).

8.4 Pediatric Use

Of the 155 patients undergoing liver surgery who were treated in adequate and well-controlled studies of EVICEL* Fibrin Sealant (Human), in which EVITHROM is a component, eight were pediatric patients. Of these, five were less than 2 years old and three were between 2 and 12 years old. Use of EVITHROM in pediatric patients is supported by these data and by extrapolation of findings for safety and efficacy in adults.

8.5 Geriatric Use

Sixty three (63) subjects over 65 years of age received EVITHROM in the phase III clinical trial. No differences in safety or effectiveness were observed between the elderly and younger patients. Greater susceptibility of older patients to adverse reactions cannot be ruled out.

11. DESCRIPTION

EVITHROM Thrombin, Topical (Human) is a sterile solution, pH 6.8-7.2, containing highly purified human thrombin for the activation of clotting. Thrombin is a highly specific protease that transforms fibrinogen into fibrin.

Frozen EVITHROM consists of a white to slightly yellowish opaque mass. When thawed, EVITHROM is clear to slightly opalescent and colorless to slightly yellowish.

The composition of EVITHROM is as follows:

Active Ingredients:

Human thrombin (800-1200 IU/ml)

Other Ingredients:

Calcium chloride, Human albumin, Mannitol, Sodium acetate, Water for injection (WFI)

EVITHROM is made from pooled Human Source Plasma obtained from US licensed plasma collection centers.

Individual plasma units obtained for production of EVITHROM are tested by FDA-licensed serological tests for HBsAg, HIV 1 & 2 Ab and HCV Ab as well as FDA-licensed Nucleic Acid Testing (NAT) methods for HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests.

Additionally, the plasma is tested by NAT for HAV and HBV and must be negative. Since the effectiveness of these test methods in detecting low levels of viral material is still under investigation, the significance of a negative result for these viruses is unknown. NAT for parvovirus B19 is also performed and the level of contamination is not permitted to exceed 10,000 copies/ml. This limit is applied to restrict the viral load of parvovirus B19 in the starting plasma pool.

In addition to the screening of plasma units, each manufacturing pool is tested for HBsAg, HIV-1 & 2 Ab, HCV Ab, and for HCV NAT. Manufacturing pool testing, however, is of lower sensitivity than individual unit testing.

EVITHROM is manufactured by chromatographic purification of prothrombin from cryo-poor plasma followed by activation with calcium chloride. The manufacturing process includes two targeted steps for inactivation or removal of viruses. The first of these is treatment with a solvent/detergent (S/D) mixture (1% tri-n-butyl phosphate, 1% Triton X-100) for 6 hours at 26°C to inactivate lipid enveloped viruses.

The S/D reagents are removed by cation exchange chromatography. Mannitol and human albumin are used to stabilize the solution, which undergoes nanofiltration for removal of both enveloped and non-enveloped viruses. After nanofiltration, the solution is formulated with calcium chloride, sterile filtered and aseptically filled and frozen.

The effectiveness of the S/D treatment and nanofiltration procedures for reducing virus content has been assessed using a series of viruses with a range of physico-chemical characteristics. The results of the validation studies are summarized in the following table:

Table 2: Reducing factors of S/D treatment and nanofiltration for a series of viruses

Virus	HIV-1	SBV	BVDV	PRV	EMCV	HAV	CPV
	Reduction factor (log10)						
S/D Treatment	>5.82	>5.31	>4.74	>4.25	Not Done	Not Done	0.0
Nanofiltration	>4.36	>5.32	Not Done	>5.47	6.37	6.95	5.85
Global Reduction Factor	**>10.18**	**>10.63**	**>4.74**	**>9.72**	**6.37**	**6.95**	**5.85**

HIV-1: Human Immunodeficiency Virus Type 1
SBV: Sindbis Virus
BVDV: Bovine Viral Diarrhea Virus
PRV: Pseudorabies Virus
EMCV: Encephalomyocarditis virus
HAV: Hepatitis A Virus
CPV: Canine Parvovirus

12 CLINICAL PHARMACOLOGY

EVITHROM requires no intermediate physiological agent because it clots the fibrinogen of the blood directly. Failure to clot blood occurs in the rare case where the primary clotting defect is the absence of fibrinogen itself. The speed with which thrombin clots blood is dependent upon the concentration of both thrombin and fibrinogen.

13. NONCLINICAL TOXICOLOGY

EVICEL Fibrin Sealant (Human), which includes EVITHROM as one of the active components, was classified as non-irritant in the Primary Cutaneous Irritation Test and slightly irritant in the Ocular Irritation test.

Neurotoxicity studies performed with EVITHROM or with EVICEL confirmed that intracerebral application of thrombin was not associated with any evidence of neurotoxicity.

No toxicological effects due to solvent/detergent reagents [tri-n-butyl phosphate (TnBP) and Triton X-100] used in the virus inactivation procedure are expected since the residual levels are less than 5μg/ml.

Reproductive studies performed in rats with the combination of TnBP and Triton X-100 at doses up to approximately 600-fold human dose of TnBP (900 mg/kg/day) and 3000-fold human dose of Triton X-100 (4500 mg/kg/day) resulted in increased post-implantation loss and an increased number of late resorptions. Other studies performed with combinations of TnBP (300-fold human dose, 450 mg/kg/day) and Triton X-100 (1500-fold human dose, 2250 mg/kg/day) resulted in increased resorption rates, decreased fetal body weights, and an increased number of runts. No embryo-fetal adverse effects were observed at doses up to 300 mg/kg/day TnBP and 1500 mg/kg/day Triton X-100, 200-fold and 1000-fold the human dose, respectively.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of EVITHROM due to the human origin of thrombin. The effect of EVITHROM on fertility has not been evaluated.

Studies performed in bacteria to determine mutagenicity of human thrombin alone, TnBP alone or Triton X-100 alone were negative at all concentrations tested. All concentrations of the combination of TnBP and Triton X-100 also tested negative in assays performed to determine mammalian cell mutagenicity, chromosomal aberrations and micronuclei induction.

14 CLINICAL STUDIES

EVITHROM was compared with bovine thrombin in a phase III, prospective, randomized, controlled, double-blinded study of 305 subjects at 22 centers in the US. Subjects undergoing elective cardiovascular, neurologic (spinal) or general surgical procedures were randomized (stratified by surgical specialty) when there was oozing or bleeding of mild intensity that could not be controlled by other surgical techniques and the surgeon determined that a topical hemostatic agent was necessary. Bovine thrombin and EVITHROM were applied with SURGIFOAM* Absorbable Gelatin Sponge, USP.

Treatment with EVITHROM was as successful as treatment with bovine thrombin in achieving the primary efficacy endpoint: hemostasis within 10 minutes of product application and secondary efficacy endpoints: hemostasis within 6 and 3 minutes of product application.

Table 3: Efficacy for Intent to Treat (ITT) population

Time Interval	Treatment Group: # Successes/N (%)		Ratio Human/Bovine	95% CI for Ratio Human/Bovine[1,2]
	EVITHROM N=153	Bovine Thrombin N=152		
10 minutes	149/153 (97.4)	148/152 (97.4)	1.00	0.96, 1.05
6 minutes	145/153 (94.8)	141/152 (92.8)	1.02	0.96, 1.09
3 minutes	112/153 (73.2)	110/152 (72.4)	1.01	0.88, 1.16

[1] 95% CI is for the ratio of proportions of success
[2] For the two treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

Table 4: Efficacy at 6 minutes (ITT population)

Surgical Specialty	Treatment Group: # Successes/N (%)		Ratio Human/Bovine	95% CI for Ratio Human/Bovine[1,2]
	Human Thrombin	Bovine Thrombin		
Cardiovascular	44/47 (93.6)	38/46 (82.6)	1.13	0.97, 1.36
Neurosurgical (Spine)	60/61 (98.4)	59/60 (98.3)	1.00	0.93, 1.08
General Surgery	41/45 (91.1)	44/46 (95.7)	0.95	0.82, 1.08
Overall	145/153 (94.8)	141/152 (92.8)	1.02	0.96, 1.09

[1] 95% CI is for the ratio of proportions of success
[2] For the two treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

At the 6 minute and 10 minute time points, >90% of subjects from all surgeries in both study groups had achieved hemostasis. The following results were documented for the 3 minute time point as stratified by surgery and study treatment: (1) cardiovascular surgery- human thrombin: 61.7%; bovine thrombin: 63.0%, (2) spinal surgery- human thrombin: 83.6%; bovine thrombin: 80.0%, (3) general surgery- human thrombin: 71.1%; bovine thrombin: 71.7%. for an overall ratio of proportions of 1.01.

16 HOW SUPPLIED/STORAGE AND HANDLING

EVITHROM is supplied in the following single-use packages, each containing 800-1200 IU/ml Thrombin, Topical (Human):

- Vial containing 2 ml, 5 ml or 20 ml frozen solution

Storage and handling

Store frozen vials at -18°C or colder for up to 2 years.

Unopened vials can be stored at 2°C to 8°C for up to 30 days.

EVITHROM has been shown to be stable for up to 24 hours at room temperature.

Do not use after the expiration date stated on the box or after 30 days if stored at 2°C to 8°C after thawing.

Do not re-freeze EVITHROM once it has been thawed.

Do not refrigerate EVITHROM once at room temperature. Discard unused product after 24 hours at room temperature.

Discard if the packaging of EVITHROM is damaged.

17 PATIENT COUNSELING INFORMATION

Some viruses such as hepatitis A virus and parvovirus B19 are particularly difficult to remove or inactivate. Parvovirus B19 most seriously affects pregnant women or immune-compromised individuals. Symptoms of parvovirus B19 infection include: fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, fatigue and low-grade fever followed by nausea, vomiting and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

If absorbed systemically EVITHROM could potentially cause blood clotting disorders. Patients should be encouraged to consult their physician for any new or unusual symptoms.

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