

# *Surgiflo*<sup>®</sup> *hemostatic matrix*

## **Technical Report**



**ETHICON**<sup>™</sup> | Biosurgery

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1. Woodworth B, Chandra R, LeBenger J, Ilie B, Schlosser R. A gelatin–thrombin matrix for hemostasis after endoscopic sinus surgery. *American Journal of Otolaryngology —Head and Neck Medicine and Surger.* 30(2009) 49-53.

## IV. Prescribing Information

1. SURGIFLO® Hemostatic Matrix
2. EVITHROM® Thrombin, Topical (Human) – Frozen
3. EVITHROM® Thrombin, Topical (Human) – Lyophilized

### *Indications and Usage*

EVITHROM® is a topical thrombin indicated 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 (such as suture, ligature or cautery) is ineffective or impractical. EVITHROM® may be used in conjunction with an Absorbable Gelatin Sponge, USP.

### *Important Safety Information*

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

There is a potential risk of thrombosis if absorbed systemically.

Anaphylactic reactions may occur.

The most common adverse reactions during clinical trial (reported in at least 2% of subjects treated with EVITHROM®) were prolonged activated partial thromboplastin time, increased INR, decreased lymphocyte count, prolonged prothrombin time and increased neutrophil count. Adverse events were reported in the clinical trial with similar frequency in the two study groups (EVITHROM® or bovine thrombin group)

# I. Description and Physical Properties

## 1. Device Description

The SURGIFLO® Hemostatic Matrix is a sterile, absorbable porcine gelatin paste intended for hemostatic use by applying to a bleeding surface. The matrix is supplied in a prefilled syringe to be mixed with 2-5 milliliters of additional liquid (saline or thrombin). It absorbs completely, with little tissue reaction, within 4 to 6 weeks following application when excessive amounts are not used.

The porcine gelatin used to make SURGIFLO® is derived from pig skins. The gelatin is processed to yield a 100% gelatin powder product. The powder is then processed to yield the SURGIFOAM® powder paste distributed as SURGIFLO® Hemostatic Matrix.

The SURGIFLO® Hemostatic Matrix is supplied in two configurations:

### 1. A tray containing:

- 1 x 12 mL syringe pre-filled with 6 mL hemostatic matrix
- 1 x 12 mL (empty) sterile syringe
- 1 applicator tip (white)
- 1 flexible applicator tip (blue) with gauge marker lines and numbers
- 1 syringe luer adapter
- 1 liquid transfer cup

### 2. A kit containing:

- 1 x 12 mL syringe pre-filled with 6 c hemostatic matrix
- 1 x 12 mL (empty) sterile syringe
- 1 applicator tip (white)
- 1 flexible applicator tip (blue) with gauge marker lines and numbers
- 1 syringe luer adapter
- 1 liquid transfer cup
- 2,000 IU lyophilized human thrombin powder for reconstitution
- 10 mL Water for Injection, USP
- 1 x 3 mL syringe

The SURGIFLO® Hemostatic Matrix itself has a one-year shelf life. In the kit configuration, the lyophilized thrombin powder has a two year shelf life when stored at 2-25C (36-77F), the kit in its entirety has a one-year shelf life.

The pre-filled matrix is off-white in appearance, and is mixed with either 2-5 mL of either sterile saline or thrombin. Mixing is facilitated by using the sterile empty syringe, a luer adapter, and liquid transfer cup included in the packaging. Once the hemostatic matrix is mixed with the additional liquid, an applicator tip is attached to the syringe for product delivery onto a bleeding site. The final product is a flowable gelatin matrix that allows intimate contact with bleeding surfaces.

SURGIFOAM® Sponge is marketed outside the US under the international trade name of SPONGOSTAN® and has been in use clinically for over 50 years. SURGIFOAM® has been subjected to clinical testing in the United States in randomized, controlled, clinical trials. The powder form has been available in the US since September, 2002.

## 2. Mechanism of Action

SURGIFLO® Hemostatic Matrix has hemostatic properties. The flowable gelatin matrix component provides a matrix for blood platelets to adhere to and to aggregate within, initiating the patient's natural hemostatic cascade. The patient's endogenous thrombin is activated, and the patient's thrombin converts endogenous fibrinogen in their bloodstream into an insoluble fibrin clot. When exogenous thrombin is used as the additional fluid for mixing SURGIFLO®, it provides an ancillary effect to the innate hemostatic property of the flowable gelatin matrix component.

## 3. Manufacturing Process

SURGIFOAM® Sponge material is cross-linked and hardened by treatment with dry heat to render it insoluble in water. The hardened gelatin sponges are then milled into a powder and discharged through a sieve. The resulting SURGIFOAM® powder and a liquid component are mixed and then foamed to form a gelatin paste which is filled into a syringe and capped. This final paste is known as SURGIFLO® Hemostatic Matrix.

The prefilled syringe containing the SURGIFLO® Hemostatic Matrix is placed into a PETG Blister tray to form a kit. The other components of the kit include the empty syringe, female-female luer connector, applicator tip and mixing cup. The blister tray is covered with a labeled coated TYVEK lid and sealed. The tray is then placed within a pouch (TYVEK and a see-through polymeric film). The tray and pouch are sealed using heat and pressure. The package is then subject to Cobalt 60 sterilization.

## 4. Indications

SURGIFLO® Hemostatic Matrix, saturated with sterile solution, is indicated for surgical procedures (except ophthalmic) for hemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical.

Although not necessary, SURGIFLO® Hemostatic Matrix can be used with or without thrombin to achieve hemostasis.

## 5. Contraindications

Do not use SURGIFLO® Hemostatic Matrix in closure of skin incisions because it may interfere with the healing of skin edges. This interference is due to mechanical interposition of gelatin and is not secondary to intrinsic interference with wound healing.

Do not use SURGIFLO® Hemostatic Matrix in intravascular compartments because of the risk of embolization.

Do not use SURGIFLO® Hemostatic Matrix in patients with known allergies to porcine gelatin.

## 6. Warnings

SURGIFLO® Hemostatic Matrix is not intended as a substitute for meticulous surgical technique and the proper application of ligatures or other conventional procedures for hemostasis.

SURGIFLO® Hemostatic Matrix should not be used in the presence of infection. SURGIFLO® Hemostatic Matrix should be used with caution in contaminated areas of the body. If signs of infection or abscess develop where SURGIFLO® Hemostatic Matrix has been positioned, reoperation may be necessary in order to remove the infected material and allow drainage.

SURGIFLO® Hemostatic Matrix should not be used in instances of pumping arterial hemorrhage. It should not be used where blood or other fluids have pooled or in cases where the point of hemorrhage is submerged.

SURGIFLO® Hemostatic Matrix will not act as a tampon or plug in a bleeding site, nor will it close off an area of blood collecting behind a tampon.

Excess SURGIFLO® Hemostatic Matrix should be removed if possible once hemostasis has been achieved because of the possibility of dislodgement of the device or compression of other nearby anatomic structures.

SURGIFLO® Hemostatic Matrix should be removed from the site of application when used in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm. Care should be exercised to avoid overpacking.

SURGIFLO® Hemostatic Matrix may swell creating the potential for nerve damage.

The safety and effectiveness of SURGIFLO® Hemostatic Matrix for use in ophthalmic procedures has not been established.

SURGIFLO® Hemostatic Matrix should not be used for controlling post-partum intrauterine bleeding or menorrhagia.

The safety and effectiveness of SURGIFLO® Hemostatic Matrix has not been established in children and pregnant women.

## 7. Precautions

Caution: Safe and effective use of SURGIFOAM® Sponge has been reported in a published neurologic retrospective study involving 1700 cases in Europe. Safe and effective use in neurosurgery has not been proven through randomized, controlled clinical studies in the United States.

Caution: SURGIFLO® Hemostatic Matrix is supplied as a sterile product and cannot be re-sterilized. Unused open pouches of SURGIFLO® Hemostatic Matrix should be discarded.

Caution: While packing a cavity for hemostasis is sometimes surgically indicated, SURGIFLO® Hemostatic Matrix should not be used in this manner unless excess product that is not needed to maintain hemostasis is removed. When mixed according to the Instructions for Use, SURGIFLO® Hemostatic Matrix may swell approximately 19% on average upon contact with additional fluid.

Caution: Only the minimum amount of SURGIFLO® Hemostatic Matrix needed to achieve hemostasis should be used. Once hemostasis has been achieved, any excess SURGIFLO® Hemostatic Matrix should be carefully removed.

Caution: SURGIFLO® Hemostatic Matrix should not be used in conjunction with autologous blood salvage circuits. It has been demonstrated that fragments of collagen based hemostatic agents may pass through 40µ transfusion filters of blood scavenging systems.

Caution: SURGIFLO® Hemostatic Matrix should not be used in conjunction with methylmethacrylate adhesives. Microfibrillar collagen has been reported to reduce the strength of methylmethacrylate adhesives used to attach prosthetic devices to bone surfaces.

Caution: SURGIFLO® Hemostatic Matrix should not be used for the primary treatment of coagulation disorders.

Caution: Although the safety and effectiveness of the combined use of SURGIFLO® Hemostatic Matrix with other agents such as topical thrombin, antibiotic solution or antibiotic powder has not been evaluated in controlled clinical trials, if in the physician's judgment, concurrent use of topical thrombin or other agents is medically advisable, the product literature for that agent should be consulted for complete prescribing information.

Caution: The safety and effectiveness for use in urological procedures has not been established through a randomized clinical study.

Caution: In urological procedures, SURGIFLO® Hemostatic Matrix should not be left in the renal pelvis or ureters to eliminate the potential foci for calculus formation.

## 8. Adverse Events

A total of 142 patients received SURGIFOAM® Sponge during a clinical trial comparing SURGIFOAM® Sponge to another absorbable gelatin sponge. The most common adverse events recorded during and after the application of the device were fever, tachycardia, and asthenia (a general feeling of weakness). Table 1 lists those adverse events that occurred in greater than 5% of the SURGIFOAM® Sponge patients. The control patients are included for comparison. Other adverse events observed in less than 5% of the SURGIFOAM® Sponge patients were chest pain, somnolence, anorexia, anxiety, dizziness, ecchymosis, oliguria, abdominal pain, thrombocytopenia, agitation, bradycardia, confusion, depression, dyspnea, back pain, urine retention, abdominal enlargement, dry mouth, GI discomfort, dehydration, lung edema, flatulence, abnormal healing, hematuria, hiccups, hyperventilation, ileus, infection of the urinary tract, leukocytosis, vertigo, amblyopia, arrhythmia, cardiomegaly, cellulitis, chills, V dysphagia, hyperglycemia, urinary incontinence, melena, mucous membrane discharge, eye pain and pneumonia.

**In general, the following adverse events have been reported with the use of absorbable porcine gelatin-based hemostatic agents:**

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- Giant cell granulomas have been observed at implant sites when used in the brain.
- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid have been observed.
- Multiple neurologic events were reported when absorbable gelatin-based hemostatic agents were used in laminectomy operations, including cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence.
- The use of absorbable gelatin-based hemostatic agents during the repair of dural defects associated with laminectomy and craniotomy operations, have been associated with fever, infection, leg paresthesias, neck and back pain, bladder and bowel incontinence, cauda equina syndrome, neurogenic bladder, impotence, and paresis.
- The use of absorbable gelatin-based hemostatic agents have been associated with paralysis, due to device migration into foramina in the bone around the spinal cord, and blindness, due to device migration in the orbit of the eye, during lobectomy, laminectomy and repair of a frontal skull fracture and lacerated lobe.
- Foreign body reactions, “encapsulation” of fluid, and hematoma have been observed at implant sites.
- Excessive fibrosis and prolonged fixation of a tendon have been reported when absorbable gelatin-based sponges were used in severed tendon repair.
- Toxic shock syndrome was reported in association with the use of absorbable gelatinbased hemostats in nasal surgery.
- Fever, failure of absorption, and hearing loss have been observed when absorbable hemostatic agents were used during tympanoplasty.

**Table 1: Incidence of Treatment Emergent Adverse Events by Treatment Group.**

<b>TERM</b>	<b>SURGIFOAM (n=142)</b>	<b>Control Sponge (n=139)</b>	<b>Total (n=281)</b>
Fever	28 (19.7%)	34 (24.5%)	62 (22.1%)
Tachycardia	27 (19.0%)	28 (20.1%)	55 (19.6%)
Asthenia	25 (17.6%)	17 (12.2%)	42 (14.9%)
Peripheral Edema	20 (14.1%)	20 (14.4%)	40 (14.2%)
Hypertonia	20 (14.1%)	12 (8.6%)	32 (11.4%)
Anemia	19 (13.4%)	11 (7.9%)	30 (10.7%)
Nausea	18 (12.7%)	22 (15.8%)	40 (14.2%)
Constipation	17 (12.0%)	17 (12.2%)	34 (12.1%)
Hypertension	16 (11.3%)	12 (8.6%)	28 (10.0%)
Insomnia	16 (11.3%)	13 (9.4%)	29 (10.3%)
Pain	13 (9.2%)	17 (12.2%)	30 (10.7%)
Pharyngitis	13 (9.2%)	11 (7.9%)	24 (8.5%)
Vomiting	13 (9.2%)	8 (5.8%)	21 (7.5%)
Edema	12 (8.5%)	10 (7.2%)	22 (7.8%)
Pruritus	12 (8.5%)	10 (7.2%)	22 (7.8%)
Rash	12 (8.5%)	19 (13.7%)	31 (11.0%)
Headache	11 (7.7%)	9 (6.5%)	20 (7.1%)
Hypokalemia	11 (7.7%)	10 (7.2%)	21 (7.5%)
Hypomagnesemia	11 (7.7%)	11 (7.9%)	22 (7.8%)
Infection	11 (7.7%)	6 (4.3%)	17 (6.0%)
Paresthesia	11 (7.7%)	7 (5.0%)	18 (6.4%)
Dyspepsia	10 (7.0%)	4 (2.9%)	14 (5.0%)
Hypotension	10 (7.0%)	10 (7.2%)	20 (7.1%)
Diarrhea	9 (6.3%)	8 (5.8%)	17 (6.0%)
Hypocalcemia	9 (6.3%)	9 (6.5%)	18 (6.4%)
Cough Increased	8 (5.6%)	9 (6.5%)	17 (6.0%)
Edema General	8 (5.6%)	5 (3.6%)	13 (4.6%)
Hematoma	8 (5.6%)	9 (6.5%)	17 (6.0%)

## 9. Preparation Time

An internal study was designed to assess the preparation time required for SURGIFLO® Hemostatic Matrix.

### Procedure:

Two person teams representing the sterile and non-sterile operating room nurses read the instructions for use prior to participating in the timed measurement. The teams used 5 mL vials of sterile saline which was poured into a transfer cup and then utilized in SURGIFLO® preparation according to the instructions in the package insert which are as follows:

1. Draw 2-5 mL of sterile saline or thrombin solution into the empty sterile syringe.
2. Remove the cap from the end of the pre-filled syringe.
3. Attach the luer adapter to the pre-filled syringe and attach the liquid solution-containing syringe to the other end of the luer adapter.
4. Begin mixing the two components by injecting the liquid solution into the pre-filled matrix.
5. Continue to mix the components by pushing the combined material back and forth between the syringes until the consistency is even (this will require approximately 5-6 transfers).
6. Once mixed, 8-11 mL of hemostatic matrix should reside completely in one syringe. Remove the empty syringe and the luer adapter.
7. Attach an applicator tip to the filled syringe.

Assembly time was measured from the point of pouring the sterile solution into the transfer cup to the point where the product with applicator tip attached was ready to be handed to the surgeon (step 7).

Six replicates of the timed preparation were performed by six different two person teams.

### Results:

Team No.	Start Time	Stop Time (in seconds)	Total Time (in seconds)
1	0	23	23 sec
2	0	30	30 sec
3	0	28	28 sec
4	0	18	18 sec
5	0	21	21 sec
6	0	23	23 sec

## 10. Product Yield

Each tray/kit contains 6cc of SURGIFLO® Hemostatic Matrix and the final product yield depends on the amount of additional liquid added, as follows:

Starting Amount of SURGIFLO®	Additional Liquid Added for Mixing	Final Product Yield
6 mL	2 mL	8 mL
6 mL	3 mL	9 mL
6 mL	4 mL	10 mL
6 mL	5 mL	11 mL

## 11. Applicator Tip Characteristics

### Flex Tip

Design verification studies were completed to ensure the addition of the flexible tip did not affect the ergonomics of the device.

#### Measurements and Observations:

- The force to express SURGIFLO® from the syringe through the Flex Tip while straight
- The force to express SURGIFLO® from the syringe through the Flex Tip while bent to a 90° angle
- During expression, the tip was inspected to ensure it remained in place
- After expression through the bent tip, the tip was inspected to ensure that the flex angle was maintained.

#### Results:

Sample	Expression Force through Straight Tip (lbs)	Expression Force through Bent Tip (lbs)
1	2.3	2.2
2	2.0	1.8
3	1.3	2.1
4	1.8	2.3
5	1.8	1.8
6	1.9	1.9
7	1.8	1.9
8	2.0	1.5
9	1.4	1.9
10	2.0	2.0

#### Conclusions:

The average expression force through the straight tip was 1.8 lbs (SD 0.3) and through the bent tip was 2.0 lbs (SD 0.2) which was significantly less than the predefined maximum specification of 13.0 lbs. All tips remained in place and at the same angle during expression of the SURGIFLO®. The use of the Flex Tip is therefore not expected to create any difficulties in use.

Reference: BE 2006 0250

## II. Physical Testing

### 1. Toxicity

To confirm that the SURGIFLO® Hemostatic Matrix causes no local or systemic toxicity issues, a subchronic toxicity study was conducted. This study was an intraperitoneal toxicity study in rats that examined 4 and 12-week endpoints.

It included histopathology of the intraperitoneal injection site as well as representative organ systems (liver, kidney, stomach, small and large intestine, bladder, cecum, spleen, heart, lung, uterus). Dose selection was based on surgeon interviews that indicated a maximum of twelve packages of material might be used in a single procedure. There was no evidence of local or systemic toxicity in this study.

In compliance with FDA-GLP regulations, SURGIFLO® was tested for material mediated pyrogenicity, acute systemic toxicity, and intracutaneous reactivity. In all cases, there was no evidence of toxicity.

The use of thrombin with SURGIFLO® Hemostatic Matrix components does not present any toxicity concerns. Thrombin has been used extensively with gelatin sponges and powders in numerous surgical applications such as bone bleeding, needle suture hole bleeding and general applications (Harris et al., 1978; Lundblad et al., 2004).

References: PSE 04-0152

PMA Supplement P990004/S008 March 9, 2005

Harris WH, Crothers OD, Moyon BJ and Bourne RB (1978). Topical hemostatic agents for bone bleeding in humans: A comparison of gelatin paste, gelatin sponge plus bovine thrombin and microfibrillar collagen. *J. Bone Joint Surg Am.* Vol 60(4), 454-456.

Lundblad RL et al. (2004). A review of the therapeutic uses of thrombin. *Thromb Haemost.* Vol 91(5), 851-860.

## 2. Absorption

In order to characterize the absorption profile of SURGIFLO®, two different absorption/tissue reaction studies were conducted. The first study was a longer-term intraperitoneal study using the worst-case scenario of 12 packages of material being used during a single procedure. It examined the absorption of SURGIFLO® from the abdominal cavity over 26 week duration with interim time points. By 8 weeks, SURGIFLO® was essentially absorbed. As indicated in the package insert, SURGIFLO® is absorbed within 4-6 weeks when used in appropriate amounts, in this study the volume was excessive and therefore additional time was required for absorption.

The second study was an intramuscular implantation study that examined the absorption of a single dose of SURGIFLO®. Histopathology indicated that at 6 weeks post-implantation, SURGIFLO® was completely absorbed.

References: PSE 01-0411, PSE 04-0602

## 3. Stability Studies

### Stability of the SURGIFLO® Hemostatic Matrix

To ensure that the SURGIFLO® Pre-filled Flowable Hemostat maintained its original properties over time multiple internal studies were conducted subjecting the prefilled syringe to accelerated and real-time aging.

#### Methods:

SURGIFLO® was pre-filled into a syringe and closed with an end cap to evaluate the stability of the pre-filled product itself along with any interactions with components that are in contact with the SURGIFLO® product during storage, namely the syringe components and the end cap. Product was evaluated at both 25°C/60% Relative Humidity (real time conditions) and 33°C/70% Relative Humidity (accelerated aging conditions) and exposed to -20°C/ambient Relative Humidity for 24 hours to determine the effects of freezing on the product. Properties assessed included visual evaluations of color change, granulation, and phase separation, and functional evaluations of expression force and swine spleen hemostatic efficacy. Samples were assessed at 3.5 months and 7 months of aging under the respective conditions of temperature and humidity. Aged samples were not expected to differ from baseline samples in any visual or functional evaluation.

#### Results:

No aged samples differed significantly from baseline samples in any functional evaluations.

No aged samples except the 7 month/33°C differed from baseline samples in any visual criteria. The 7 month/33°C samples did not meet the visual criterion for color change. These samples were yellow in color; however when additional saline was added to the matrix per the Instructions for Use, the color returned to the original white color as seen in the baseline samples.

Reference: Stability Study No. 1230B Rev B.

### **Stability of SURGIFLO® Accessory Components**

To ensure that accessory components supplied in the SURGIFLO® trays maintain their original properties over time an internal study was conducted subjecting them to accelerated and real time aging. Accessory components included the syringe, syringe cap, luer connector, flange extension, transfer cup and applicator.

#### **Methods:**

Components were manufactured using tooling and processes representative of the final production process and all components were visually inspected prior to evaluation to look for signs of adverse events, such as, but not limited to cracking. Components were sterilized with gamma sterilization utilizing a minimum dose of 30kGy. After sterilization, any additional packaging was performed per the applicable Manufacturing Process Instruction (MPI). Samples were placed in film/film pouches and tests were performed in sequential order. All aged devices were to maintain their original function and comply with the approved product specification.

#### **Results:**

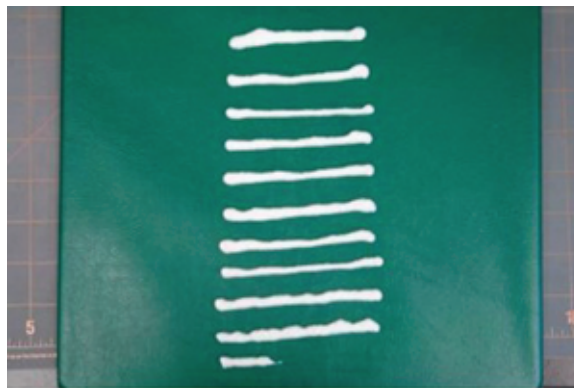
Visual tests performed indicated that acceptance criteria were met for all samples for both baseline and one-year real time equivalent (RTE) samples.

**References:** Stability Study No. 1230C, Ver 1, Revised 12/04/2004

BE-2004-1184

## **4. Consistency of SURGIFLO®**

An internal study was conducted to demonstrate the consistency of SURGIFLO®. SURGIFLO® was mixed with thrombin solution according to the IFU and the resulting paste was expressed through the applicator tip onto a flat surface and photographed. The SURGIFLO® product was consistent from beginning to end as shown in the photos below.



#### **Conclusions:**

SURGIFLO®, when mixed with thrombin solution, produced a uniform and consistent paste throughout the syringe.

#### **Reference:**

SURGIFLO® Hemostatic Matrix with Thrombin: Thrombin Activity and Final Product Consistency; October 25, 2009

## 5. Use with Thrombin Studies

### A. Activity of Thrombin in the Presence of SURGIFLO®

An internal evaluation was conducted to determine the activity of thrombin when mixed with SURGIFLO® Hemostatic Matrix as measured by a coagulation assay over a 24-hour time period.

#### Procedure:

Four SURGIFLO® product syringes were selected from the same lot and prepared according to the following steps for evaluation:

1. Human thrombin, 2 mL was aspirated in a separate syringe; then utilizing a connection device it was mixed with the SURGIFLO® syringe back and forth for six passes. Pushing the plunger of the syringe containing the human thrombin to the gelatin containing syringe constituted “one pass.”
2. 0.1 g samples of the SURGIFLO® and Human Thrombin mixture were placed into four scintillation vials. Five mL of saline solution were added to each vial then mixed then a small aliquot of sample was transferred to the coagulation analyzer.

Samples were stored in syringe, at room temperature, until time of testing. Aliquots were obtained from the same four syringes at each testing time.

Coagulation assays were executed to determine the activity of human thrombin mixed with SURGIFLO® product over time. Analysis was conducted utilizing a thrombin calibration curve with standards being prepared and run at each time point.

#### Results:

Average thrombin activity results over 24 hours were as follows:

Time	Average Thrombin Activity (IU/g)
0 Hours	385
4 Hours	356
8 Hours	358
24 Hours	363

#### Conclusions:

The hemostatic activity of thrombin in the presence of SURGIFLO® Hemostatic Matrix did not change significantly throughout the 24-hour time period. Variations in activity were within the detection limits of the assay.

**Reference:** 24 Hour Thrombin Activity in SURGIFLO® Note to File

### B. Hemostatic Efficacy of SURGIFLO® plus Thrombin versus SURGIFLO® plus saline

An internal evaluation was conducted to compare the hemostatic efficacy of SURGIFLO® Hemostatic Matrix when mixed with 2 mL of Human Thrombin, 5 mL of Human Thrombin, and 5 mL of saline.

#### Procedure:

1. A mid-line incision was made on an anesthetized and surgically prepared pig to expose the spleen.
2. Wounding of the spleen was created for test or control article application via 6mm biopsy punch to an approximate depth of 3 mm. The splenic capsule was then removed via surgical forceps. One new site was initiated for each sample.
3. Test samples were applied to the wound sites followed by gauze. A negative control using only gauze was performed at the initiation and completion of the testing period.
4. The test sample or gauze was placed on a single wound in the spleen.
5. Digital pressure was initially applied for 30 seconds followed by a 30 second hemostasis evaluation period. If hemostasis was not achieved an additional 30-second tamponade was applied and a 30 second re-evaluation for hemostasis was performed.

6. Tamponade application and observation periods were performed until hemostasis achieved or until the testing period reached twelve minutes.

**Results:**

Test Article	TTH in seconds		
	Animal 18117	Animal 18118	Animal 18119
Negative Control - Gauze	>720	>720	
SURGIFLO® + 2 mL Human Thrombin	30	87	30
SURGIFLO® + 5 mL Human Thrombin	78	85	120
SURGIFLO® + 5 mL Saline	130	256	127
SURGIFLO® + 2 mL Human Thrombin	30	30	30
SURGIFLO® + 5 mL Human Thrombin	30	30	84
SURGIFLO® + 5 mL Saline	180	120	125
SURGIFLO® + 2 mL Human Thrombin	30	30	78
SURGIFLO® + 5 mL Human Thrombin	75	75	75
SURGIFLO® + 5 mL Saline	285	210	122
SURGIFLO® + 2 mL Human Thrombin	30	88	135
SURGIFLO® + 5 mL Human Thrombin	82	106	80
SURGIFLO® + 5 mL Saline	208	205	195
SURGIFLO® + 2 mL Human Thrombin	96	30	30
SURGIFLO® + 5 mL Human Thrombin	75	80	115
SURGIFLO® + 5 mL Saline	195	135	185
SURGIFLO® + 2 mL Human Thrombin	78	90	84
SURGIFLO® + 5 mL Human Thrombin	95	80	105
SURGIFLO® + 5 mL Saline	290	195	183
SURGIFLO® + 2 mL Human Thrombin	125	84	30
SURGIFLO® + 5 mL Human Thrombin	77	81	98
SURGIFLO® + 5 mL Saline	200	150	160
SURGIFLO® + 2 mL Human Thrombin	30	30	30
SURGIFLO® + 5 mL Human Thrombin	84	110	84
SURGIFLO® + 5 mL Saline	222	210	180
SURGIFLO® + 5 mL Human Thrombin	-	85	-
SURGIFLO® + 5 mL Saline	225	-	-
Negative Control - Gauze	>720	>720	>720

	Mean TTH (seconds)	Range (seconds)
SURGIFLO® + 2 mL Human Thrombin	57	30 - 135
SURGIFLO® + 5 mL Human Thrombin	84	30 - 120
SURGIFLO® + 5 mL Saline	188	120 - 290

## Hemostasis Proportions of Success

<b>SURGIFLO® with:</b>	<b>Hemostasis &lt; 2 minutes</b>	<b>Hemostasis &lt; 4 minutes</b>
2 mL of Thrombin	96%	100%
5 mL of Thrombin	88%	100%
5 mL of saline	0%	88%
Negative Control (gauze)	0	0

SURGIFLO® with 2 or 5 mL Human Thrombin had higher proportions of success at either 2 or 4 minutes than SURGIFLO® with 5 mL Saline.

### **Conclusion:**

The addition of thrombin improves the hemostatic efficacy of SURGIFLO® Hemostatic Matrix.

Reference: PSE 07-0004

### **C. SURGIFLO® Mixed with either 2000IU or 5000IU Thrombin**

In a preclinical hemostasis efficacy model, SURGIFLO® was mixed with either 2000IU human thrombin (in 2 mL solution), 5000IU human thrombin (in 5 mL solution), or mixed with 5 mL saline, and applied to freely bleeding punch biopsy sites in a porcine spleen. It was concluded that SURGIFLO® mixed either with 2000IU thrombin or 5000IU thrombin was more effective than SURGIFLO® mixed with 5 mL saline, based on the proportions of incisions that achieved hemostasis within 2 minutes of product application. Statistical analysis also showed that the proportion of success in achieving hemostasis of SURGIFLO® with 2 mL human thrombin is equivalent to that of SURGIFLO® with 5 mL human thrombin.

The following table demonstrates the thrombin concentration after mixing with SURGIFLO® in these two formulations.

<b>Thrombin Activity per Syringe</b>	<b>SURGIFLO® Volume</b>	<b>Thrombin Volume</b>	<b>Total Volume</b>	<b>Thrombin Activity per mL of Final Product</b>
2000IU	6 mL	2 mL	8 mL	250IU/mL
5000IU	6 mL	5 mL	11 mL	450IU/mL

In this preclinical study, SURGIFLO® with a thrombin activity of 250IU/mL is equivalent to SURGIFLO® with a thrombin activity of 450IU/mL.

Reference: PSE 07-0004

## **6. Conformability and impact on time to hemostasis**

An internal study was conducted with the purpose of evaluating the conformability of SURGIFLO® Hemostat Matrix, vs SURGIFOAM® Absorbable Gelatin Sponge in an ex vivo model.

### **Study Design:**

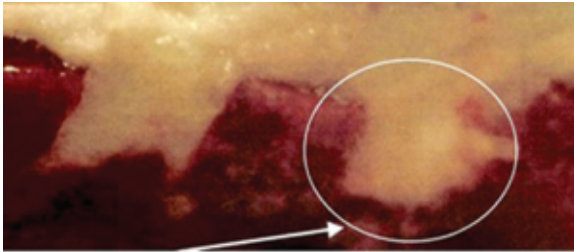
This study utilized ex vivo porcine liver tissue. Tissue defects were created using a standard 8 mm biopsy punch. Product samples were applied to multiple test sites (10 per article), and then photographs were taken from a cross-sectional perspective. Using an image analysis system, measurements of surface area exposure to each test article were made and recorded. Comparative analyses of the recorded conformability percentiles were conducted.

**Sample Preparation:**

SURGIFLO® samples were prepared by mixing an additional 5 mL of Thrombin to the supplied pre-filled syringe and applied to the biopsy site. Mixing of the Thrombin and SURGIFLO® was accomplished by connecting the supplied pre-filled syringe to an additional syringe containing the Thrombin solution via a luer connector and forcing syringe contents back and forth into each syringe 10 times.

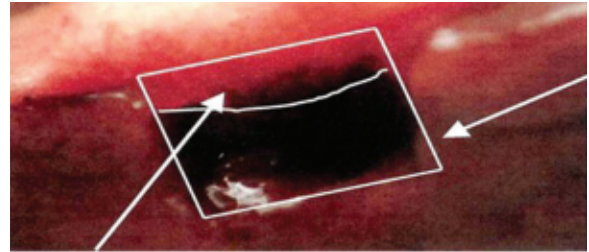
SURGIFOAM® sponge samples were cut to approximately 2.0 cm x 2.0 cm pieces. Each sponge was kneaded and soaked in Thrombin until saturated. Using fingers, excess liquid was gently squeezed from sample. The test samples were applied to the biopsy punch site and digital pressure applied for 30 seconds.

Cross section of SURGIFLO® inside 8mm biopsy defect



SURGIFLO® demonstrating 100% Surface Area Contact, indicating 100% conformability.

Cross section of SURGIFOAM® Sponge inside 8mm biopsy defect



Measurement of surface area contact of SURGIFOAM® Sponge. This example demonstrates 27% Surface Area Contact, indicating 27% conformability.

**Results:**

SURGIFLO® demonstrated significantly more surface area exposure to the defect than SURGIFOAM® Sponge.

Treatment Group	Mean Percentage Contact with Defect
SURGIFLO®	98.1
SURGIFOAM® Sponge	23.9

**Discussion:**

An increase in tissue contact by a hemostatic product may be associated with a faster time to hemostasis. Previous studies have determined that thrombin mediates clot formation in vivo and is a potent activator of fibrinogen and platelets (Pfister 2001). Therefore, a hemostatic product containing thrombin, that has greater tissue contact may be expected to demonstrate better hemostatic efficacy.

In this study, surface area of a test article inside the defect was used as a measurement for tissue contact and, thus, conformability of two different hemostatic products. In this case, it was demonstrated that an increase in conformability is directly related to a faster time to hemostasis.

Following measurement of the surface area of both sets of samples, it was found that SURGIFLO® samples demonstrated more surface area contact (Mean = 98.1%) to the defect than SURGIFOAM® Sponge samples (Mean = 23.9%) thereby indicating SURGIFLO® had a significantly greater degree of conformability.

**References:**

Pfister ME, Andrews RT, Pavcnik D, et al. Effects of Intraarterial Thrombin in the Swine Model. *J Vasc Interv Radiol*; 2001 (12): 235 - 245

## III. Literature

### 1. A gelatin-thrombin matrix for hemostasis after endoscopic sinus surgery

**Authors:** B. Woodworth, R. Chandra, J. LeBenger, B. Ilie, R. Schlosser

**Source:** *American Journal of Otolaryngology—Head and Neck Medicine and Surgery* 30(2009) 49-53

#### **Study Objective:**

The objective of this study was to evaluate the clinical performance of SURGIFLO® Hemostatic Matrix with thrombin (3-5 mL) in achieving hemostasis in patients undergoing elective primary or revision endoscopic sinus surgery for chronic sinusitis.

#### **Methods:**

Thirty patients (17 males and 13 females, average age, 48.2 ± 15.1 years) with a total of 54 operated sides at 3 institutions were evaluated in this prospective, single-arm study with a four-month enrollment period.

Patients were 18 years of age or older and undergoing elective primary or revision endoscopic sinus surgery for chronic sinusitis (nonpolypoid chronic sinusitis, nonallergic nasal polyposis, allergic fungal sinusitis, and other) with a bleeding surface requiring hemostasis.

Patients were excluded for the following reasons: pregnancy; morbid obesity; uncontrolled diabetes; long-term oral steroid or chemotherapeutic agent use; inflammatory, systemic or immunodeficiency disease; bleeding diathesis or coagulopathy; known antibodies to bovine thrombin, sensitivity to porcine gelatin or bovine components; or acute local infections and severe bleeding at the operative site.

The primary endpoint, hemostasis within 10 minutes of product application, was evaluated following application of SURGIFLO® Hemostatic Matrix with a single-barrel syringe held in place with a cottonoid pledget. Once hemostasis was achieved, the pledget was removed and excess SURGIFLO® Hemostatic Matrix was removed. Bleeding was graded on a scale of 1 (none to minimal bleeding with no suction required) to 5 (bleeding out of the nostril upon removal of suction)

Patient satisfaction data including pain and nasal pressure/congestion on a scale of 10 were collected at the 7-day follow-up visit. Postoperative healing assessments were recorded at the 30-day follow-up visit and included evaluation for the presence of mucosal regeneration, mucosal edema, and need for debridement. Serious adverse events were also evaluated.

#### **Outcomes Measured:**

1. Time to hemostasis (including manual compression time)
2. Patient satisfaction (pain and pressure/nasal congestion)
3. Post-Operative healing

#### **Results:**

1. **Hemostasis:** Twenty-nine patients achieved hemostasis within 10 minutes of product application (96.7%; 1-sided 95% CI, 85.1%-100%).

The median time to hemostasis for all operative sites including manual compression time was 61 seconds.

The mean estimated blood loss was 38.1 ± 41.2 mL.

One patient reported a mild rebleeding that resolved with packing.

2. **Patient Satisfaction:** Patients stated an average pain level of 2.3 of 10.

The mean level of pressure/nasal congestion was 3.2 of 10.

3. **Healing Assessments:** Mucosal regeneration was achieved fully or partially for all 54 operative sites at 30 days. None of the operative sites exhibited residual SURGIFLO® Hemostatic Matrix.

**Adverse Events:**

No serious adverse events or complications such as synechiae, adhesion, or infection, were reported.

**Study Limitations:** Not a randomized controlled trial.

**Key Takeaways:**

1. The popularity of absorbable nasal packing after endoscopic sinus surgery over traditional nasal packing has increased as patients demand less painful postoperative care.
2. When surgeons applied SURGIFLO® Hemostatic Matrix to the site of bleeding in this study and held in place with a cottonoid pledget, the median time to hemostasis was 61 seconds, with 96.7% of bleeding sides achieving hemostasis within 10 minutes.
3. No significant synechiae, adhesions, or infections were reported.

## Essential Prescribing Information

### SURGIFLO®

Hemostatic Matrix (Made from SURGIFOAM® Absorbable Gelatin Sponge U.S.P.)

plus FlexTip

#### INTENDED USE/INDICATIONS

SURGIFLO Hemostatic Matrix, saturated with sterile solution, is indicated for surgical procedures (except ophthalmic) for hemostasis, when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical.

Although not necessary, SURGIFLO Hemostatic Matrix can be used with or without thrombin to achieve hemostasis.

#### CONTRAINDICATIONS

Do not use SURGIFLO Hemostatic Matrix in closure of skin incisions because it may interfere with the healing of skin edges. This interference is due to mechanical interposition of gelatin and is not secondary to intrinsic interference with wound healing.

Do not use SURGIFLO Hemostatic Matrix in intravascular compartments because of the risk of embolization.

Do not use SURGIFLO Hemostatic Matrix in patients with known allergies to porcine gelatin.

#### WARNINGS

- SURGIFLO Hemostatic Matrix is not intended as a substitute for meticulous surgical technique and the proper application of ligatures or other conventional procedures for hemostasis.
- SURGIFLO Hemostatic Matrix should not be used in the presence of infection. SURGIFLO Hemostatic Matrix should be used with caution in contaminated areas of the body. If signs of infection or abscess develop where SURGIFLO Hemostatic Matrix has been positioned, reoperation may be necessary in order to remove the infected material and allow drainage.
- SURGIFLO Hemostatic Matrix should not be used in instances of pumping arterial hemorrhage. It should not be used where blood or other fluids have pooled or in cases where the point of hemorrhage is submerged. SURGIFLO Hemostatic Matrix will not act as a tampon or plug in a bleeding site, nor will it close off an area of blood collecting behind a tampon.
- SURGIFLO Hemostatic Matrix should be removed if possible once hemostasis has been achieved because of the possibility of dislodgment of the device or compression of other nearby anatomic structures.
- SURGIFLO Hemostatic Matrix should be removed from the site of application when used in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm. Care should be exercised to avoid overpacking. SURGIFLO Hemostatic Matrix may swell creating the potential for nerve damage.
- The safety and effectiveness of SURGIFLO Hemostatic Matrix for use in ophthalmic procedures has not been established.
- SURGIFLO Hemostatic Matrix should not be used for controlling post-partum intrauterine bleeding or menorrhagia.
- The safety and effectiveness of SURGIFLO Hemostatic Matrix has not been established in children and pregnant women.

#### PRECAUTIONS

- Caution:** Safe and Effective use of SURGIFOAM Sponge has been reported in a published Neurologic retrospective study involving 1700 cases in Europe. Safe and Effective use in neurosurgery has not been proven through randomized, controlled clinical studies in the United States.
- Caution:** SURGIFLO Hemostatic Matrix is supplied as a sterile product and cannot be re-sterilized. Unused open pouches of SURGIFLO Hemostatic Matrix should be discarded.
- Caution:** While packing a cavity for hemostasis is sometimes surgically indicated, SURGIFLO Hemostatic Matrix should not be used in this manner unless excess product that is not needed to maintain hemostasis is removed. When mixed according to the Instructions for Use, SURGIFLO Hemostatic Matrix may swell approximately 19 % upon contact with additional fluid.
- Caution:** Only the minimum amount of SURGIFLO Hemostatic Matrix needed to achieve hemostasis should be used. Once hemostasis is achieved, any excess SURGIFLO Hemostatic Matrix should be carefully removed.
- Caution:** SURGIFLO Hemostatic Matrix should not be used in conjunction with autologous blood salvage circuits. It has been demonstrated that fragments of collagen based hemostatic agents may pass through 40µ transfusion filters of blood scavenging systems.
- Caution:** SURGIFLO Hemostatic Matrix should not be used in conjunction with methylmethacrylate adhesives. Microfibrillar collagen has been reported to reduce the strength of methylmethacrylate adhesives used to attach prosthetic devices to bone surfaces.
- Caution:** SURGIFLO Hemostatic Matrix should not be used for the primary treatment of coagulation disorders.
- Caution:** Although the safety and effectiveness of the combined use of SURGIFLO Hemostatic Matrix with other agents such as topical thrombin, antibiotic solution or antibiotic powder has not been evaluated in controlled clinical trials, if in the physician's judgment, concurrent use of topical thrombin or other agents is medically advisable, the product literature for that agent should be consulted for complete prescribing information.
- Caution:** The safety and effectiveness for use in urological procedures has not been established through a randomized clinical study.
- Caution:** In urological procedures, SURGIFLO Hemostatic Matrix should not be left in the renal pelvis or ureters to eliminate the potential foci for calculus formation.

#### ADVERSE EVENTS

A total of 142 patients received SURGIFOAM Sponge during a clinical trial comparing SURGIFOAM Sponge to another absorbable gelatin sponge. The most common adverse events recorded during and after the application of the device were fever, tachycardia, and asthenia (a general feeling of weakness). Table 1 lists those adverse events that occurred in greater than 5% of the SURGIFOAM Sponge patients. The control patients are included for comparison. Other adverse events observed in less than 5% of the SURGIFOAM Sponge patients were chest pain, somnolence, anorexia, anxiety, dizziness, ecchymosis, oliguria, abdominal pain, thrombocytopenia, agitation, bradycardia, confusion, depression, dyspnea, back pain, urine retention, abdominal enlargement, dry mouth, GI discomfort, dehydration, lung edema, flatulence, abnormal healing, hematuria, hiccups, hyperventilation, ileus, infection of the urinary tract, leukocytosis, vertigo, amblyopia, arrhythmia, cardiomegaly, cellulitis, chills, V dysphagia, hyperglycemia, urinary incontinence, melena, mucous membrane discharge, eye pain and pneumonia.

In general, the following adverse events have been reported with the use of absorbable porcine gelatin-based hemostatic agents:

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- Giant cell granulomas have been observed at implant sites when used in the brain.
- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid have been observed.
- Multiple neurologic events were reported when absorbable gelatin-based hemostatic agents were used in laminectomy operations, including cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence.
- The use of absorbable gelatin-based hemostatic agents during the repair of dural defects associated with laminectomy and craniotomy operations, have been associated with fever, infection, leg paresthesias, neck and back pain, bladder and bowel incontinence, cauda equina syndrome, neurogenic bladder, impotence, and paresis.
- The use of absorbable gelatin-based hemostatic agents have been associated with paralysis, due to device migration into foramina in the bone around the spinal cord, and blindness, due to device migration in the orbit of the eye, during lobectomy, laminectomy and repair of a frontal skull fracture and lacerated lobe.
- Foreign body reactions, "encapsulation" of fluid, and hematoma have been observed at implant sites.
- Excessive fibrosis and prolonged fixation of a tendon have been reported when absorbable gelatin-based sponges were used in severed tendon repair.
- Toxic shock syndrome was reported in association with the use of absorbable gelatin-based hemostats in nasal surgery.
- Fever, failure of absorption, and hearing loss have been observed when absorbable hemostatic agents were used during tympanoplasty.

**Table 1:** Incidence of Treatment Emergent Adverse Events by Treatment Group.

TERM	SURGIFOAM (n=142)	Control Sponge (n=139)	Total (n=281)
Fever	28 (19.7%)	34 (24.5%)	62 (22.1%)
Tachycardia	27 (19.0%)	28 (20.1%)	55 (19.6%)
Asthenia	25 (17.6%)	17 (12.2%)	42 (14.9%)
Peripheral Edema	20 (14.1%)	20 (14.4%)	40 (14.2%)
Hypertonia	20 (14.1%)	12 (8.6%)	32 (11.4%)
Anemia	19 (13.4%)	11 (7.9%)	30 (10.7%)
Nausea	18 (12.7%)	22 (15.8%)	40 (14.2%)
Constipation	17 (12.0%)	17 (12.2%)	34 (12.1%)
Hypertension	16 (11.3%)	12 (8.6%)	28 (10.0%)
Insomnia	16 (11.3%)	13 (9.4%)	29 (10.3%)
Pain	13 (9.2%)	17 (12.2%)	30 (10.7%)
Pharyngitis	13 (9.2%)	11 (7.9%)	24 (8.5%)
Vomiting	13 (9.2%)	8 (5.8%)	21 (7.5%)
Edema	12 (8.5%)	10 (7.2%)	22 (7.8%)
Pruritus	12 (8.5%)	10 (7.2%)	22 (7.8%)
Rash	12 (8.5%)	19 (13.7%)	31 (11.0%)
Headache	11 (7.7%)	9 (6.5%)	20 (7.1%)
Hypokalemia	11 (7.7%)	10 (7.2%)	21 (7.5%)
Hypomagnesemia	11 (7.7%)	11 (7.9%)	22 (7.8%)
Infection	11 (7.7%)	6 (4.3%)	17 (6.0%)
Paresthesia	11 (7.7%)	7 (5.0%)	18 (6.4%)
Dyspepsia	10 (7.0%)	4 (2.9%)	14 (5.0%)
Hypotension	10 (7.0%)	10 (7.2%)	20 (7.1%)
Diarrhea	9 (6.3%)	8 (5.8%)	17 (6.0%)
Hypocalcemia	9 (6.3%)	9 (6.5%)	18 (6.4%)
Cough Increased	8 (5.6%)	9 (6.5%)	17 (6.0%)
Edema General	8 (5.6%)	5 (3.6%)	13 (4.6%)
Hematoma	8 (5.6%)	9 (6.5%)	17 (6.0%)

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 P.O. Box 151, Somerville,  
 NJ 08876-0151 USA

Manufactured by  
 Ferrosan A/S  
 Sydmarken 5, DK-2860 Soeborg  
 Denmark

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### EVITHROM® Thrombin, Topical (Human)

Frozen solution for Topical Use Only

Initial U.S. approval: 2007

#### INDICATIONS AND USAGE

- EVITHROM® is a topical thrombin indicated 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 (such as suture, ligature or cautery) is ineffective or impractical (1).
- EVITHROM® may be used in conjunction with an Absorbable Gelatin Sponge, USP (7).

#### DOSAGE AND ADMINISTRATION

- Frozen solution for topical use only. DO NOT INJECT (2.2).**
- The amount of EVITHROM® 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 EVITHROM® prior to use in one of the following ways (2.1):

- 2°C to 8°C (refrigerator): vials thaw within 1 day; or
- 20°C to 25°C (room temperature): vials thaw within 1 hour; or
- 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.

The time between thawing and application is restricted to 24 hours at room temperature (16).

- Vials are for single use only. Discard unused contents (2.2).

#### DOSAGE FORMS AND STRENGTHS

- EVITHROM® is supplied in vials of 2 ml, 5 ml or 20 ml frozen solution containing 800-1200 units/ml of Thrombin, Topical (Human) (3).

The potency expressed in units is determined using a clotting assay against an internal reference standard for potency that has been calibrated against the World Health Organisation (WHO) Second International Standard for Thrombin, 01/580. Therefore, a unit used herein is equivalent to an International Unit.

#### FULL PRESCRIBING INFORMATION: CONTENTS<sup>1</sup>

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
  - Thawing Prior to Application
  - Application Techniques
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
  - Potential Risks
- ADVERSE REACTIONS
  - Clinical Trials Experience
  - Post Marketing Experience
- DRUG INTERACTIONS
- USE IN SPECIFIC POPULATIONS
  - Pregnancy
  - Labor and Delivery

#### 1. INDICATIONS AND USAGE

EVITHROM® Thrombin, Topical (Human) is indicated 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 (such as suture, ligature or cautery) 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; or
- 20°C to 25°C (room temperature): vials thaw within 1 hour; or
- 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

Use EVITHROM® topically. Apply only on the surface of bleeding tissue. DO NOT INJECT.

##### EVITHROM® alone

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

##### EVITHROM® in conjunction with Absorbable Gelatin Sponge, USP

- Transfer EVITHROM® into a sterile container using aseptic techniques.
- Immerse gelatin sponge of desired shape in the EVITHROM® solution.
- Vigorously knead the sponge with moistened gloved fingers until all air is expelled and it can return to its original size and shape.
- 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 units/ml of Thrombin, Topical (Human).

The potency expressed in units is determined using a clotting assay against an internal reference standard for potency that has been calibrated against the World Health Organisation (WHO) Second International Standard for Thrombin, 01/580. Therefore, a unit used herein is equivalent to an International Unit.

#### 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 Potential Risks

Because this product is made from human plasma, it may carry a risk of transmitting

#### 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 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 (5.1).
- Potential risk of thrombosis if absorbed systemically (5.2).

#### 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](http://www.fda.gov/medwatch).

#### USE IN SPECIFIC POPULATIONS

- Pregnancy: Animal data are summarized in the Non Clinical Toxicology section (13). No data in pregnant women. EVITHROM® should only be used in pregnancy if clearly indicated (8.1).

#### See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2009

- Nursing Mothers
- Pediatric Use
- Geriatric Use
- OVERDOSAGE
- DESCRIPTION
- CLINICAL PHARMACOLOGY
  - Mechanism of Action
  - Pharmacodynamics
  - Pharmacokinetics
- NONCLINICAL TOXICOLOGY
  - Carcinogenesis, Mutagenesis, Impairment of Fertility
  - Animal toxicology and/or pharmacology
- CLINICAL STUDIES
- HOW SUPPLIED/STORAGE AND HANDLING
- PATIENT COUNSELING INFORMATION

<sup>1</sup> Sections or subsections omitted from the full prescribing information are not listed

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. The physician should discuss the risks and benefits of this product with the patient. 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](http://www.fda.gov/medwatch).

Potential risk of thrombosis if absorbed systemically

#### 6. ADVERSE REACTIONS

##### 6.1 Clinical Trials Experience

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.

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

System Organ Class/Adverse Event	Thrombin Type		
	EVITHROM® (n=153)	Bovine (n=152)	Total (n=305)
<b>Investigations</b>	<b>11 (7.2%)</b>	<b>14 (9.2%)</b>	<b>25 (8.2%)</b>
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%)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>1 (0.7%)</b>	<b>3 (2.0%)</b>	<b>4 (1.3%)</b>
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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> with incidence of antibody development following administration of other products may be misleading and the clinical significance of these findings is unknown.

### 6.2 Post Marketing Experience

No adverse reactions have been identified from domestic or spontaneous reports, including class related products.

### 7. DRUG INTERACTIONS

No drug interactions are known.

### 8. USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Teratogenic effects: Pregnancy category C.

Adequate and well-controlled studies in pregnant women have not been performed. EVITHROM<sup>®</sup> 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<sup>®</sup> 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).

#### 8.2 Labor and Delivery

The safety of EVITHROM<sup>®</sup> for use during labor and delivery has not been established.

#### 8.3 Nursing Mothers

The safety of EVITHROM<sup>®</sup> for use during breast-feeding has not been established. Use only if clearly needed.

#### 8.4 Pediatric Use

Of the 155 patients undergoing liver surgery who were treated in adequate and well-controlled studies of EVICEL<sup>®</sup> Fibrin Sealant (Human), in which EVITHROM<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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.

### 10. OVERDOSAGE

No case of overdose has been reported.

### 11. DESCRIPTION

EVITHROM<sup>®</sup> 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<sup>®</sup> consists of a white to slightly yellowish opaque mass. When thawed, EVITHROM<sup>®</sup> is clear to slightly opalescent and colorless to slightly yellowish. The composition of EVITHROM<sup>®</sup> is as follows:

#### Active Ingredients:

Human thrombin (800-1200 units/ml)

#### Other Ingredients:

Calcium chloride, Human albumin, Mannitol, Sodium acetate, Water for injection (WFI) EVITHROM<sup>®</sup> is made from pooled Human Source Plasma obtained from US licensed plasma collection centers.

Individual plasma units obtained for production of EVITHROM<sup>®</sup> are tested by licensed serological tests for HBsAg, HIV 1 & 2 Ab and HCV Ab. Additionally, the plasma units are tested by licensed Nucleic Acid Testing (NAT) for HIV-1, HCV, HBV, HAV and parvovirus 19. All tests for HIV, HCV, HBV and HAV must be negative (non-reactive). However, since the effectiveness of the HBV and HAV NAT methods in detecting low levels of viral material is still under investigation, the significance of a negative result for these viruses is unknown. The level of parvovirus B19 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, and for HCV NAT. Manufacturing pool testing, however, is of lower sensitivity than individual unit testing.

EVITHROM<sup>®</sup> 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)	
								>5.82	>5.31
SD 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<sup>®</sup> 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.

#### 12.1 Mechanism of Action

Thrombin (coagulation factor IIa) is a highly specific protease that transforms plasma fibrinogen into fibrin which, in the presence of Factor XIII in the patient's plasma, is cross-linked to form a stable clot. When applied to a surgical wound where bleeding is present, thrombin activates fibrinogen in the patient's plasma to form fibrin, which results in clot formation and hemostasis. The fibrin clot is stabilized by cross-linking occurring as a result of activation of the patient's endogenous factor XIII, which requires the presence of calcium.

#### 12.2 Pharmacodynamics

Clinical pharmacodynamic studies with Human Thrombin have not been performed as this would be ethically unacceptable with this type of product.

### 12.3 Pharmacokinetics

Due to the nature of the product, intended for topical application to the surface of tissue at the surgical site, pharmacokinetic studies were not conducted.

### 13. NONCLINICAL TOXICOLOGY

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 µg/kg/day) and 3000-fold human dose of Triton X-100 (4500 µg/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 µg/kg/day) and Triton X-100 (1500-fold human dose, 2250 µg/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 µg/kg/day TnBP and 1500 µg/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<sup>®</sup> due to the human origin of thrombin. Studies were performed in bacteria to determine mutagenicity of human thrombin alone, and solvent/detergent residues [tri-n-butyl phosphate (TnBP) and Triton X-100, used in the virus inactivation manufacturing step. These studies were negative for both Thrombin and for TnBP or Triton X-100 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.

The effect of EVITHROM<sup>®</sup> on fertility has not been evaluated. Reproductive studies were performed in rats with the combination of solvent detergent impurities, TnBP and Triton X-100 at doses up to approximately 600-fold human dose of TnBP (900 µg/kg/day) and 3000-fold human dose of Triton X-100 (4500 µg/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 µg/kg/day) and Triton X-100 (1500-fold human dose, 2250 µg/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 µg/kg/day TnBP and 1500 µg/kg/day Triton X-100, 200-fold and 1000-fold the human dose, respectively.

#### 13.2 Animal Toxicology and/or Pharmacology

EVICEL<sup>®</sup> Fibrin Sealant (Human), which includes EVITHROM<sup>®</sup> 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<sup>®</sup> or with EVICEL<sup>®</sup> 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.

### 14. CLINICAL STUDIES

EVITHROM<sup>®</sup> 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<sup>®</sup> were applied with SURGIFOAM<sup>®</sup> Absorbable Gelatin Sponge, USP. Treatment with EVITHROM<sup>®</sup> 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 <sup>1,2</sup>
	EVITHROM <sup>®</sup> 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

<sup>1</sup> 95% CI is for the ratio of proportions of success

<sup>2</sup> 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 <sup>1,2</sup>
	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

<sup>1</sup> 95% CI is for the ratio of proportions of success

<sup>2</sup> 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<sup>®</sup> is supplied in the following single-use packages, each containing 800-1200 units/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<sup>®</sup> 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<sup>®</sup> once it has been thawed.

Do not refrigerate EVITHROM<sup>®</sup> once at room temperature. Discard unused product after 24 hours at room temperature.

Discard if the packaging of EVITHROM<sup>®</sup> 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 immunocompromised 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<sup>®</sup> could potentially cause blood clotting disorders. Patients should be encouraged to consult their physician for any new or unusual symptoms.

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

### EVITHROM, Thrombin, Topical (Human)

For Topical Use Only, Lyophilized Powder for Reconstitution  
Initial U.S. Approval: 2007

#### INDICATIONS AND USAGE

- EVITHROM is a topical thrombin indicated 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 (such as suture, ligature or cautery) is ineffective or impractical (1).
- EVITHROM may be used in conjunction with an Absorbable Gelatin Sponge, USP (1).

#### DOSAGE AND ADMINISTRATION

- Lyophilized powder for reconstitution for topical use only. DO NOT INJECT (2.2).**
- The amount of EVITHROM required depends upon the area of tissue to be treated and the method of application. In clinical studies, volumes up to 10ml were used in conjunction with Absorbable Gelatin Sponge, USP (2.2).
- Reconstitute in 2ml Water for Injection, USP (2.1). Reconstituted solution can be stored at room temperature for up to 8 hours and should be used within that time period (16).
- Vials are for single use only. Discard unused contents (2.2).

#### DOSAGE FORMS AND STRENGTHS

EVITHROM is supplied in vials containing 2000 (1600-2400) units of lyophilized human thrombin powder for reconstitution. When reconstituted with 2 ml of Water for Injection, USP, the final solution contains 1000 (800-1200) units/ml of EVITHROM (3).

The potency expressed in units is determined using a clotting assay against an internal reference standard for potency that has been calibrated against the World Health Organisation (WHO) Second International Standard for Thrombin, 01/580. Therefore, a unit used herein is equivalent to an International Unit.

#### CONTRAINDICATIONS

- Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products (4).
- Do not use for treatment of severe or brisk arterial bleeding (4).

#### WARNINGS AND PRECAUTIONS

- Potential risk of thrombosis if absorbed systemically (5.1).
- 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 (5.2).

#### ADVERSE REACTIONS

- The most common adverse reactions during clinical trial (reported in at least 2% of subjects treated with EVITHROM) were prolonged activated partial thromboplastin time, increased INR, decreased lymphocyte count, prolonged prothrombin time and increased neutrophil count. Adverse events were reported in the clinical trial with similar frequency in the two study groups (EVITHROM or bovine thrombin group) (6).
- Anaphylactic reactions may occur (6).
- 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](http://www.fda.gov/medwatch).

#### USE IN SPECIFIC POPULATIONS

Pregnancy: Animal data are summarized in the Non Clinical Toxicology section (13). No data in pregnant women. EVITHROM should only be used in pregnancy if clearly indicated (8.1).

#### See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2009

#### FULL PRESCRIBING INFORMATION: CONTENTS\*

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- DOSAGE AND ADMINISTRATION
  - Reconstitution Prior to Application
  - Application Techniques
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
  - Thrombosis
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\*Sections or subsections omitted from the full prescribing information are not listed

#### 1 INDICATIONS AND USAGE

EVITHROM<sup>®</sup>, Thrombin, Topical (Human), is indicated 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 (such as suture, ligature or cautery) is ineffective or impractical.

EVITHROM<sup>®</sup>, Thrombin, Topical (Human), may be used in conjunction with an Absorbable Gelatin Sponge, USP.

#### 2 DOSAGE AND ADMINISTRATION

##### FOR TOPICAL USE ONLY. DO NOT INJECT.

The amount of EVITHROM<sup>®</sup> required depends upon the area of tissue to be treated and the method of application.

##### 2.1 Reconstitution Prior to Application

Reconstitute the lyophilized human thrombin powder.

Use aseptic technique when handling vials and syringes.

- Remove the flip-off plastic cap from the vial to expose the rubber stopper.
- Using a sterile needle and syringe, add 2 ml of Water for Injection, USP to the glass vial.
- Shake gently until the solution is clear.

Reconstituted solution is stable for up to 8 hours at room temperature and should be used within this time period.

##### 2.2 Application Techniques

DO NOT INJECT. Use EVITHROM<sup>®</sup> topically.

Apply only on the surface of bleeding tissue.

##### EVITHROM<sup>®</sup> alone

- Sponge target surface (do not wipe) or suction free of blood before application.
- The surface may be flooded with EVITHROM<sup>®</sup> using a sterile syringe and small gauge needle.
- After treatment, avoid sponging the clot to assure that it remains securely in place.

##### EVITHROM<sup>®</sup> in conjunction with Absorbable Gelatin Sponge, USP

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

The amount of EVITHROM<sup>®</sup> 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<sup>®</sup> was used in conjunction with Absorbable Gelatin Sponge, USP.

Vials are for single use only. Discard unused contents.

#### 3 DOSAGE FORMS AND STRENGTHS

EVITHROM<sup>®</sup> is supplied in a vial containing 2000 (1600-2400) units of lyophilized human thrombin powder for reconstitution. When reconstituted with 2ml of Water for Injection, USP the final solution contains 1000 (800-1200) units/ml of Thrombin, Topical (Human). The potency expressed in units is determined using a clotting assay against an internal reference standard for potency that has been calibrated against the World Health Organisation (WHO) Second International Standard for Thrombin, 01/580. Therefore, a unit used herein is equivalent to an International Unit.

#### 4 CONTRAINDICATIONS

- 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 Thrombosis

Potential risk of thrombosis if absorbed systemically

##### 5.2 Transmission of Infectious Agents

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. The physician should discuss the risks and benefits of this product with the patient.

#### 6 ADVERSE REACTIONS

The most common adverse reactions during clinical trials (reported in at least 2% of subjects treated with EVITHROM<sup>®</sup>) were prolonged activated partial thromboplastin time, increased INR, decreased lymphocyte count, prolonged prothrombin time and increased neutrophil count.

##### 6.1 Clinical Trials Experience

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.

In a phase III multicenter, prospective, controlled, randomized, double-blinded study of 305 subjects where EVITHROM<sup>®</sup> (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 (see Table 1). 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<sup>®</sup> 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<sup>®</sup> group experienced a treatment emergent severe adverse event: respiratory arrest and post-procedural hematoma (in one subject) and extracranial hematoma. Three subjects in the bovine thrombin group experienced a treatment emergent severe adverse event: hyperhidrosis, pyrexia and post-procedural hematoma.

No deaths were reported during the study period.

Viral serology was not monitored during the study with EVITHROM<sup>®</sup>. 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

System Organ Class/Adverse Event	Thrombin Type		
	EVITHROM <sup>®</sup> (n=153)	Bovine (n=152)	Total (n=305)
<b>Investigations</b>	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%)
<b>Skin and Subcutaneous Tissue Disorders</b>	1 (0.7%)	3 (2.0%)	4 (1.3%)
Pruritis	1 (0.7%)	3 (2.0%)	4 (1.3%)
<b>General Disorders and Administration Site Conditions</b>	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<sup>®</sup> (frozen formulation) 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<sup>®</sup> 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 thrombin, bovine thrombin, human Factor V/Va or bovine Factor V/Va following administration of EVITHROM<sup>®</sup> with incidence of antibody development following administration of other products may be misleading and the clinical significance of these findings is unknown.

## 6.2 Post Marketing Experience

No adverse reactions have been identified from spontaneous post-marketing reports.

## 7 DRUG INTERACTIONS

No drug interactions are known.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Teratogenic effects: Pregnancy category C.

Adequate and well-controlled studies in pregnant women have not been performed. EVITHROM<sup>®</sup> 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<sup>®</sup> 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).

### 8.2 Labor and Delivery

The safety of EVITHROM<sup>®</sup> for use during labor and delivery has not been established.

### 8.3 Nursing Mothers

The safety of EVITHROM<sup>®</sup> for use during breast-feeding has not been established. Use only if clearly needed.

### 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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.

## 10 OVERDOSAGE

No case of overdose has been reported.

## 11 DESCRIPTION

EVITHROM<sup>®</sup> is provided as a sterile powder of purified human thrombin. The lyophilized powder is white to slightly yellowish in color. When reconstituted, EVITHROM<sup>®</sup> solution, pH 6.8-7.2, is clear to slightly opalescent and colorless to slightly yellowish in color. The composition of the lyophilized powder of EVITHROM<sup>®</sup> is as follows:

### Active Ingredients:

Human Thrombin (1600-2400 units)

### Other Ingredients:

Calcium chloride, Human albumin, Mannitol, Sodium acetate

EVITHROM<sup>®</sup> is made from pooled Human Source and Recovered Plasma obtained from US licensed plasma collection centers. Individual plasma units obtained for production of EVITHROM<sup>®</sup> are tested by licensed serological tests for HBsAg, HIV 1 & 2 Ab and HCV Ab and recovered plasma units are also tested for HTLV I/II. Additionally, the plasma units are tested by licensed Nucleic Acid Testing (NAT) for HIV-1, HCV, HBV, HAV and parvovirus 19. All tests for HIV, HCV, HBV and HAV must be negative (non-reactive). However, since the effectiveness of the HBV and HAV NAT methods in detecting low levels of viral material is still under investigation, the significance of a negative result for these viruses is unknown. The level of parvovirus B19 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, and for HCV NAT. Manufacturing pool testing, however, is of lower sensitivity than individual unit testing.

EVITHROM<sup>®</sup> 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 Table 2:

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)	
								SD Treatment	Nanofiltration
SD 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<sup>®</sup> 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.

### 12.1 Mechanism of Action

Thrombin (coagulation factor IIa) is a highly specific protease that transforms plasma fibrinogen into fibrin which, in the presence of Factor XIII in the patient's plasma, is cross-linked to form a stable clot. When applied to a surgical wound where bleeding is present, thrombin activates fibrinogen in the patient's plasma to form fibrin, which results in clot formation and hemostasis. The fibrin clot is stabilized by cross-linking occurring as a result of activation of the patient's endogenous factor XIII, which requires the presence of calcium.

## 12.2 Pharmacodynamics

Clinical pharmacodynamic studies with Human Thrombin have not been performed as this would be ethically unacceptable with this type of product.

## 12.3 Pharmacokinetics

Due to the nature of the product, intended for topical application to the surface of tissue at the surgical site, pharmacokinetic studies were not conducted.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of EVITHROM<sup>®</sup> due to the human origin of thrombin.

Studies were performed in bacteria to determine mutagenicity of human thrombin alone, and solvent/detergent residues [tri-n-butyl phosphate (TnBP) and Triton X-100, used in the virus inactivation manufacturing step. These studies were negative for both thrombin and for TnBP or Triton X-100 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.

The effect of EVITHROM<sup>®</sup> on fertility has not been evaluated. Reproductive studies were performed in rats with the combination of solvent detergent impurities, TnBP and Triton X-100 at doses up to approximately 600-fold human dose of TnBP (900 µg/kg/day) and 3000-fold human dose of Triton X-100 (4500 µg/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 µg/kg/day) and Triton X-100 (1500-fold human dose, 2250 µg/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 µg/kg/day TnBP and 1500 µg/kg/day Triton X-100, 200-fold and 1000-fold the human dose, respectively.

### 13.2 Animal Toxicology and/or Pharmacology

EVICEL Fibrin Sealant (Human), which includes EVITHROM<sup>®</sup> 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<sup>®</sup> 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.

## 14 CLINICAL STUDIES

EVITHROM<sup>®</sup> was compared with bovine thrombin in a phase III multicenter, 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<sup>®</sup> were applied with SURGIFOAM<sup>®</sup> Absorbable Gelatin Sponge, USP. Treatment with EVITHROM<sup>®</sup> 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 <sup>1,2</sup>
	EVITHROM <sup>®</sup>	Bovine thrombin		
	N=153	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

<sup>1</sup> 95% CI is for the ratio of proportions of success

<sup>2</sup> 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 <sup>1,2</sup>
	EVITHROM <sup>®</sup>	Bovine thrombin		
	N=153	N=152		
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

<sup>1</sup> 95% CI is for the ratio of proportions of success

<sup>2</sup> 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<sup>®</sup> is supplied in a 2 ml vial containing 2000 (1600-2400) units of lyophilized human thrombin powder for reconstitution in 2 ml Water for Injection, USP

### Storage and handling

- Store EVITHROM<sup>®</sup> powder vials at 2-25°C (36-77°F) for up to 2 years.
- Store reconstituted EVITHROM<sup>®</sup> solution at room temperature for up to 8 hours.
- Do not use after the expiration date stated on the vial.
- Do not freeze or refrigerate EVITHROM<sup>®</sup> once it has been reconstituted.
- Vials are for single use only. Discard unused contents.
- Discard if the packaging of EVITHROM<sup>®</sup> is damaged.
- Keep the vials protected from light.

## 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 immunocompromised 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. Consult your physician if such symptoms appear.

If absorbed systemically EVITHROM<sup>®</sup> could potentially cause blood clotting disorders. Consult your physician for any new or unusual symptoms.

**ETHICON<sup>™</sup>**

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