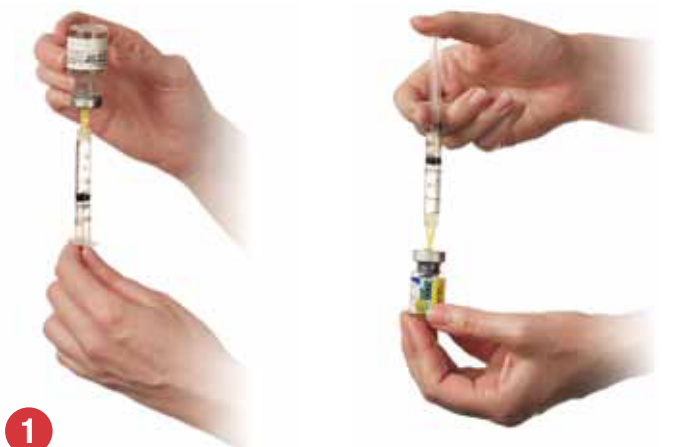


How to prepare SURGIFLO[®] Hemostatic Matrix Kit:



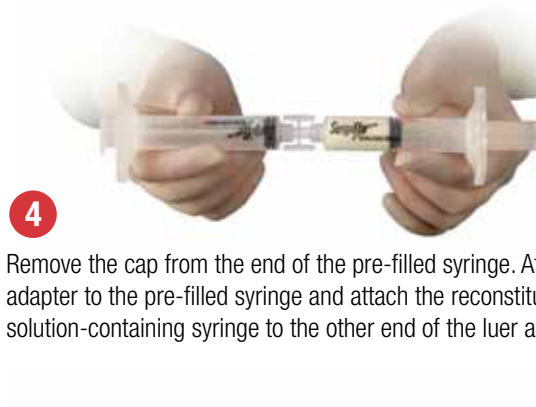
1
Remove the flip-off caps from vials to expose the rubber stopper. Using a sterile needle and syringe, add 2 mL of Water for Injection, USP to glass vial. Shake gently until the solution is clear.



2
Transfer reconstituted thrombin solution into a sterile container using aseptic technique.



3
Draw 2 mL of reconstituted thrombin solution into the empty sterile syringe.



4
Remove the cap from the end of the pre-filled syringe. Attach the luer adapter to the pre-filled syringe and attach the reconstituted thrombin solution-containing syringe to the other end of the luer adapter.



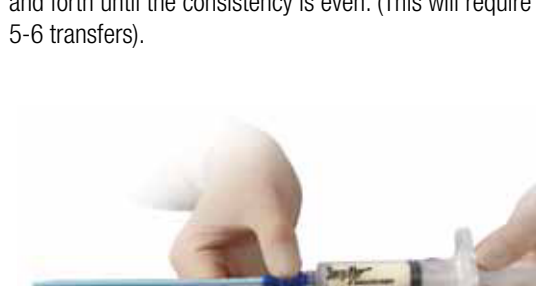
5
Begin mixing the 2 components by injecting the reconstituted thrombin solution into the pre-filled matrix.



6
Continue to mix the components by pushing the combined material back and forth until the consistency is even. (This will require approximately 5-6 transfers).



7
Once mixed, 8 mL of hemostatic matrix should reside completely in one syringe. Remove the empty syringe and the luer adapter.



8
Attach the applicator tip to the filled syringe. The product is now ready for clinical use.

The bioresorbable gelatin matrix with proven efficacy, safety, and convenience*^{1,2}

- Stops bleeding in 2 minutes or less when used with thrombin²
- Bioresorbable within 4-6 weeks¹
- Ready to use in 30 seconds or less once liquid thrombin is delivered to the sterile field*³

SURGIFLO[®] Hemostatic Matrix Kit Contents[†]

SURGIFLO[®] Hemostatic Matrix Device Thrombin Component

- One vial of 2000 units lyophilized thrombin

Additional Contents

- Tracking labels (4)
- Mixing Instructions

To order Surgiflo[®] Hemostatic Matrix Kit, call **1-800-255-2500**.
For technical support, call **1-877-384-4266**.
For additional information, visit www.ethicon360.com
Ethicon, Inc.



Indications and Usage

EVITHROM[®] Thrombin, (Topical) Human 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.⁴

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.⁴

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).⁴

Please see package inserts for EVITHROM[®] Full Prescribing Information.

Surgiflo[®]
hemostatic
matrix kit

*Bioresorbable within 4-6 weeks.¹

[†]Not a complete listing of contents.

References: 1. Full Prescribing Information for SURGIFLO[®] Hemostatic Matrix. Ethicon, Inc. 2. In vivo animal model. Data on file, Ethicon, Inc. 3. Data on file, Ethicon, Inc. 4. Full Prescribing Information. Ethicon, Inc.

Please see package insert for SURGIFLO[®] Hemostatic Matrix Kit full Prescribing Information.

For detailed instructions on preparing SURGIFLO[®] Kit please see Kit preparation instructions included in each kit.

SURGIFLO®

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

plus FlexTip

Caution: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

Do not inject into blood vessels

DESCRIPTION

The SURGIFLO Hemostatic Matrix is a sterile, absorbable porcine gelatin intended for hemostatic use by applying to a bleeding surface. The pre-filled matrix is off-white in appearance, and is mixed with either sterile saline or thrombin. Mixing is facilitated by using the enclosed accessories, included are a sterile empty syringe, a luer adapter, and a liquid transfer cup. Once the hemostatic matrix is mixed with 2-5 ml of additional liquid, an applicator tip is attached to the syringe for product delivery onto a bleeding site.

ACTIONS

SURGIFLO Hemostatic Matrix has hemostatic properties. SURGIFLO Hemostatic Matrix absorbs completely, with little tissue reaction, when excessive amounts are not used. When used in appropriate amounts SURGIFLO Hemostatic Matrix is absorbed completely within 4 to 6 weeks. In an animal implantation study, tissue reactions were classified as negligible when observed macroscopically, and moderate when observed microscopically with SURGIFOAM® Absorbable Gelatin Sponge.

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%)
Periphereal 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%)

CLINICAL STUDIES

Study Design:

An open label, randomized, controlled, multi-center, unmasked study was conducted to evaluate the safety and effectiveness of two hemostatic agents. The study compared the SURGIFLOAM Sponge to an absorbable gelatin sponge currently legally marketed in the U.S.A. The primary objective of the study was to examine the equivalence of the SURGIFLOAM Sponge to the control device as measured by hemostasis within 10 minutes of application. Cardiovascular, general surgical, and orthopedic patients were eligible for the study. The sponges were used either soaked with saline or dry. Patients were followed for two months after surgery to assess the safety of the sponge.

Study Results:

Two hundred eighty one patients were enrolled into the study and received study treatment. The hemostasis data was collected immediately during surgery and the patients were examined at two to four weeks and again at six to eight weeks in order to obtain safety data. The study effectiveness results are summarized in Table 2 below.

Table 2: Summary of Effectiveness Results Comparing SURGIFLOAM Sponge to another absorbable gelatin sponge. (Percent achieving hemostasis).

Minutes	Device	General Surgical	Cardiovascular	Orthopedic	Total
		% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)
3	SURGIFLOAM Sponge	65.6 (42/64)	57.4 (39/68)	100.0 (10/10)	64.0 (91/142)
	Control Sponge	66.2 (43/65)	62.9 (39/62)	91.7 (11/12)	66.9 (93/139)
6	SURGIFLOAM Sponge	98.4 (63/64)	80.9 (55/68)	100.0 (10/10)	90.1 (128/142)
	Control Sponge	95.4 (62/65)	91.9 (57/62)	100.0 (12/12)	94.2 (131/139)
10	SURGIFLOAM Sponge	100.0 (64/64)	89.7 (61/68)	100.0 (10/10)	95.1 (125/142)
	Control Sponge	95.4 (62/65)	96.8 (60/62)	100.0 (12/12)	96.4 (134/139)

A statistical analysis showed that SURGIFLOAM Sponge and the control sponge were equivalent in the ability to achieve hemostasis within 10 minutes. The study also collected hemostasis data at 3 and 6 minutes. These results are also summarized in Table 2.

Immune Response:

Patient sera were tested for the presence of anti-porcine collagen immunoglobulins. Sera were collected prior to surgery, at 2 to 4 weeks post surgery and at 6 to 8 weeks following surgery. Two hundred six patients were tested at baseline, 2 to 4 weeks, and at 6 to 8 weeks. Only one of the 206 patients had antibodies at baseline and 6 of the 206 patients had antibodies at the 6 to 8 week time point. Three of the patients were in the SURGIFLOAM Sponge group and 3 patients were in the control group. The analysis of the immunology data indicated that there was no difference in the ability of the SURGIFLOAM Sponge to induce antiporcine collagen immunoglobulins when compared to the control sponge.

Use of SURGIFLO* Hemostatic Matrix as a Hemostatic Agent for Nasal/Sinus Bleeding:

Surgiflo Hemostatic Matrix has been successfully used with bovine thrombin intra-operatively as a hemostatic agent for the control of bleeding post nasal sinus surgery in 30 patients (54 application sites).

Study Design:

This was a multi-center, prospective, single-arm study. Thirty (30) subjects from three (3) US centers undergoing elective endoscopic sinus surgery (ESS) who met the eligibility criteria were treated with SURGIFLO Hemostatic Matrix and bovine thrombin post ESS. Subjects were followed at 7 days (\pm 3 days) and at 30 days (\pm 7 days) post-operatively. This was a single arm study with no control arm. Patients were followed for 30 days following surgery. Post-operative healing and all complications were recorded during this period.

Study Results:

Intraoperative bleeding ceased in 29 out of 30 patients. One subject failed to achieve hemostasis within 10 minutes of product application. The median time to hemostasis for 54 operated sides including manual compression was 61 seconds. One patient had mild oozing after surgery. This patient was treated with local care with immediate resolution. No intraoperative complications, serious adverse events, or serious complication such as synechiae or infections were reported in this study.

HOW SUPPLIED

SURGIFLO Hemostatic Matrix is supplied in a kit configuration containing: 1 x 12ml syringe pre-filled with hemostatic matrix, 1 x 12ml (empty) sterile syringe, 1 applicator tip (white), 1 flexible applicator tip (blue) with marker lines and numbers, 1 syringe luer adapter, and 1 liquid transfer cup.

STORAGE AND HANDLING

SURGIFLO Hemostatic Matrix should be stored dry at controlled room temperature 36° F – 77° F (2°-25° C) It is recommended that SURGIFLO Hemostatic Matrix be used as soon as the package is opened.

DIRECTIONS FOR USE

Before using, inspect the package for signs of damage. If the package is damaged or wet, sterility cannot be assured and the contents should not be used. Sterile technique should always be used to remove the SURGIFLO Hemostatic Matrix from its packaging. Use only the minimum amount necessary to achieve hemostasis. SURGIFLO Hemostatic Matrix can be applied to the bleeding site saturated with sterile isotonic sodium chloride solution (sterile saline) or sterile topical thrombin solution. Open packages of SURGIFLO Hemostatic Matrix should be discarded, since they are not intended for reuse and/or re-sterilization.

SURGIFLO Hemostatic Matrix should be prepared using the following method:

- 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 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.
- 8) The product is now ready for clinical use.

For endoscopic sinus surgery and epistaxis:

- a. Deliver SURGIFLO Hemostatic Matrix to the source of bleeding using the selected applicator tip attached to the SURGIFLO Hemostatic Matrix syringe.
- b. Apply sufficient SURGIFLO Hemostatic Matrix to cover the entire bleeding surface.
- c. Using forceps or an appropriate instrument, carefully layer a moistened cottonoid over the SURGIFLO Hemostatic Matrix for 1-2 minutes to ensure the material remains in contact with the bleeding tissue. In cases of persistent bleeding, indicated by saturation and bleeding through the material, insert the applicator tip through the center of the mass of previously placed SURGIFLO Hemostatic Matrix to deliver fresh material as close as possible to the tissue surface. After re-application of SURGIFLO Hemostatic Matrix, use a moistened cottonoid to approximate the material to the tissue for another minute, and then inspect the site. Repeat re-application if necessary.
- d. Once hemostasis has been achieved, remove the cottonoid. If possible, excess SURGIFLO Hemostatic Matrix should be removed with gentle irrigation or careful suction. Avoid disrupting the SURGIFLO Hemostatic Matrix clot complex. The remaining SURGIFLO Hemostatic Matrix does not have to be removed, as it will be bioresorbed.
- e. Use of nasal packing is not necessary when satisfactory hemostasis is achieved.
- f. If necessary, gentle irrigation and/or careful suction can be used in postoperative period to remove the remaining SURGIFLO Hemostatic Matrix.

Caution: The use of SURGIFLO Hemostatic Matrix for mechanical support has not been studied.

Caution: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

*Trademark

Distributed by
 Johnson & Johnson
Wound Management
A division of ETHICON, INC.
P.O. Box 151, Somerville,
NJ 08876-0151 USA

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

© 2008 ETHICON, INC.
SFL-0372-09-12/10

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.

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*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Reconstitution Prior to Application
 - 2.2 Application Techniques
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Thrombosis
 - 5.2 Transmission of Infectious Agents
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
 - 6.2 Post Marketing Experience
- 7 DRUG INTERACTIONS
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Labor and Delivery

- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 10 OVERDOSAGE
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 13.2 Animal toxicology and/or pharmacology
- 14 CLINICAL STUDIES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

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

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

FOR TOPICAL USE ONLY. DO NOT INJECT.

The amount of EVITHROM® 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® topically.

Apply only on the surface of bleeding tissue.

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 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®) 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 antihistamines. 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® (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® 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.

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

Immunogenicity

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

The protocol did not specify any comparative analysis for immunogenicity data, only descriptive statistics. The adjudicated results show that 3.3% of the subjects treated with EVITHROM® (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® 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® 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® should be used in pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus. Studies to evaluate the potential reproductive/developmental toxicity of EVITHROM® have not been performed due to the human origin of thrombin. However, studies to evaluate the potential reproductive/developmental toxicity of residual levels of Triton X-100 and tri-n-butyl phosphate (solvent/detergent reagents) were conducted in animals and are summarized in the Non Clinical Toxicology section (13).

8.2 Labor and Delivery

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

8.3 Nursing Mothers

The safety of EVITHROM® 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® is a component, eight were pediatric patients. Of these, five were less than 2 years old and three were between 2 and 12 years old. Use of EVITHROM® in pediatric patients is supported by these data and by extrapolation of findings for safety and efficacy in adults.

8.5 Geriatric Use

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

10 OVERDOSAGE

No case of overdose has been reported.

11 DESCRIPTION

EVITHROM® is provided as a sterile powder of purified human thrombin. The lyophilized powder is white to slightly yellowish in color. When reconstituted, EVITHROM® 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® is as follows:

Active Ingredients:

Human thrombin (1600-2400 units)

Other Ingredients:

Calcium chloride, Human albumin, Mannitol, Sodium acetate

EVITHROM® is made from pooled Human Source and Recovered Plasma obtained from US licensed plasma collection centers. Individual plasma units obtained for production of EVITHROM® 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® 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
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® 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® 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® 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® as one of the active components, was classified as non-irritant in the Primary Cutaneous Irritation Test and slightly irritant in the Ocular Irritation test.

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

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

14 CLINICAL STUDIES

EVITHROM® 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® were applied with SURGIFOAM* Absorbable Gelatin Sponge, USP.

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

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

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

¹95% CI is for the ratio of proportions of success

²For the two treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

Table 4: Efficacy at 6 minutes (ITT population)

Surgical Specialty	Treatment Group: # Successes/N (%)		Ratio Human/Bovine	95% CI for Ratio Human/Bovine ^{1,2}
	EVITHROM®	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

¹95% CI is for the ratio of proportions of success

²For the two treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

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

16 HOW SUPPLIED/STORAGE AND HANDLING

EVITHROM® is supplied in 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® powder vials at 2-25°C (36-77°F) for up to 2 years.
- Store reconstituted EVITHROM® 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® once it has been reconstituted.
- Vials are for single use only. Discard unused contents.
- Discard if the packaging of EVITHROM® 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 immune-compromised individuals. Symptoms of parvovirus B19 infection include: fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, fatigue and low-grade fever followed by nausea, vomiting and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. Consult your physician if such symptoms appear.

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

ETHICON™

Distributed by:
ETHICON, INC.
P.O. Box 151, Somerville,
NJ 08876-0151 USA

omrix™

Manufactured by:
Omrix Biopharmaceuticals Ltd.
MDA blood bank,
Sheba Hospital, Ramat-Gan
POB 888, Kiryat Ono 55000
ISRAEL

U.S. License No. 1603
ETHICON, Inc. 2009
© Omrix Biopharmaceuticals Ltd., 2009

Art. No. 80YZ00Z3D0