Hemostasis Optimization Program

A systematic approach to bleeding

Addressing Surgical Bleeding Situations With Adjunctive Hemostats*

Intraoperative bleeding

Can you see the source of bleeding and apply hemostat?

YES

Continuous oozing
Will not stop with compression/simple packing. The solution for this bleeding is more time consuming than it is difficult.[1]

→ Oxidized regenerated cellulose (ORC) → **SURGICEL®** Absorbable Hemostats

Problematic
Even though the bleeding is accessible, it could be trouble. It is more than routine and likely to be **resistant to conventional means**, and requires immediate attention causing disruption to the normal progression of surgery.[1]

→ Fibrin patch → **EVARREST®** Fibrin Sealant Patch

NO

Difficult to access
Bleeding that occurs in **tight and irregular spaces** and you cannot see the exact source of the bleed. You are concerned accessing a tight space will cause more harm.[1]

→ Flowable gelatin → **SURGIFLO®** Hemostatic Matrix

Is there intraoperative bleeding with a concern of postoperative re-bleeding?

YES

Potential rebleeding risk
Bleeding may be addressed intraoperatively, but could later **develop into more serious complications**, especially in high-risk patients.[1]

→ Fibrin sealant → **VISTASEAL™** Fibrin Sealant (Human)

High-pressure vessel bleeding
A **leak in high-pressure vessel** (aortic orperipheral vascular suture line) that has been stopped, but if it leaks post-op, could be catastrophic.[1]

→ Vascular sealant

Please see Important Safety Information below and accompanying Full Prescribing Information for complete prescribing details.

For complete indications, contraindications, warnings, precautions, and adverse reactions, please reference full package insert.

***The bleeding situations identified reflect customer insights/market research on optimal adjunctive hemostat utilization. The product solutions should only be used in accordance with their instructions for use. Product recommendations should not supplant medical judgment. Surgeon preference, experience, and patient needs may dictate alternate technique. Review all relevant precautions, especially the indications, contraindications, warnings, and information for use. Please see package inserts for Full Prescribing Information. The visual does not reflect any sequential order in use.**

References: 1. Hemostasis Optimization Program and Next Steps Meeting , dated 06/30/2014.

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SURGIFLO® Hemostatic Matrix Essential Product Information (Made from Absorbable Gelatin Sponge, USP)

DESCRIPTION

SURGIFLO® Hemostatic Matrix is intended for hemostatic use by applying to a bleeding surface.

ACTIONS

When used in appropriate amounts SURGIFLO® Hemostatic Matrix is absorbed completely within 4 to 6 weeks.

INTENDED USE/INDICATIONS

SURGIFLO® Hemostatic Matrix, mixed with sterile saline or thrombin solution, is indicated in surgical procedures (other than ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or other conventional methods is ineffective or impractical.

CONTRAINDICATIONS

- 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.
- 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.

WARNINGS

- SURGIFLO® Hemostatic Matrix should not be used in the presence of infection and should be used with caution in contaminated areas of the body• SURGIFLO® Hemostatic Matrix should not be used in instances of pumping arterial hemorrhage. SURGIFLO® Hemostatic Matrix will not act as a tampon or plug in a bleeding site.
- 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 because it may swell resulting in nerve damage.
- Excess SURGIFLO® Hemostatic Matrix should be removed once hemostasis has been achieved.
- 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.
- The blue flexible applicator tip should not be trimmed to avoid exposing internal guidewire.
- The white straight applicator tip should be trimmed away from the surgical area. Cut a square angle to avoid creating a sharp tip.

PRECAUTIONS

- 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.
- SURGIFLO® Hemostatic Matrix is supplied as a sterile product and cannot be resterilized. • SURGIFLO® Hemostatic Matrix should not be used for packing unless excess product that is not needed to maintain hemostasis is removed. SURGIFLO® Hemostatic Matrix may swell up to 20% upon contact with additional fluid.
- SURGIFLO® Hemostatic Matrix should not be used in conjunction with autologous blood salvage circuits.
- SURGIFLO® Hemostatic Matrix should not be used in conjunction with methylmethacrylate adhesives. • 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. 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, has 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 has 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.

064302-200513

SURGICEL® Powder Absorbable Hemostat Essential Product Information

INDICATIONS

SURGICEL® Powder (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. SURGICEL® Powder can also be applied in laparoscopic or other endoscopic procedures when used with the SURGICEL™ Endoscopic Applicator.

The SURGICEL™ Endoscopic Applicator is intended for use in delivering SURGICEL® Powder absorbable hemostat to bleeding surgical sites through a 5 mm or larger trocar.

CONTRAINDICATIONS

- Do not inject or place SURGICEL® Powder into an open blood vessel. Do not use to treat bleeding from large defects in arteries or veins.
- SURGICEL® Powder should not be used to control hemorrhage from large arteries or veins.
- The SURGICEL® Powder and the SURGICEL™ Endoscopic Applicator devices were not designed for intraluminal procedures.
- When SURGICEL® Powder is used to help achieve hemostasis in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, or the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure.
- SURGICEL® Powder should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

WARNINGS

- SURGICEL® Powder is not intended for use on dry (non-bleeding) surfaces or for prevention of bleeding.
- Closing with SURGICEL® Powder in a contaminated wound without drainage may lead to complications and should be avoided.
- SURGICEL® Powder should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances.
- SURGICEL® Powder is dry and there may be difficulties in precise delivery under certain circumstances. Unintentional device placement may result in powder scattering and device migration that may increase the risk of adhesion formation. In preclinical in vivo animal studies it was demonstrated that SURGICEL® Powder does not increase the incidence of remote adhesions in laparoscopic procedures.
- Although SURGICEL® Powder is bactericidal against a wide range of pathogenic microorganisms, it is not intended as a substitute for systemically administered therapeutic or prophylactic antimicrobial agents to control or to prevent postoperative infections.
- To prevent clogging with the SURGICEL™ Endoscopic Applicator Tip, do not touch the tip to wet surface. Be careful to avoid damaging tissue with the rigid tip.
- Do not attempt to trim the applicator tip. Replace the tip if it becomes clogged.

PRECAUTIONS

- SURGICEL® Powder should not be used in conjunction with autologous blood salvage circuits, because its fragments may pass through the transfusion filters of blood-scavenging systems.
- Use only as much SURGICEL® Powder (oxidized regenerated cellulose) as is necessary and apply only where needed for hemostasis. Remove any excess before surgical closure in order to facilitate absorption and to minimize the possibility of foreign body reaction.
- Use minimal amount of SURGICEL® Powder required to achieve hemostasis, and remove excess powder in the area of drains to prevent clogging. In urological procedures, minimal amounts of SURGICEL® Powder should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.
- Since absorption of SURGICEL® Powder could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.
- If SURGICEL® Powder is used temporarily to line the cavity of open wounds, it should be removed by irrigation with sterile water or saline solution after bleeding has stopped.
- Precautions should be taken in otorhinolaryngologic surgery to ensure that none of the material is aspirated by the patient (e.g., controlling hemorrhage after tonsillectomy and controlling epistaxis).
- The applicator tip provided on the SURGICEL® Powder device is not intended for laparoscopic or other endoscopic use. If laparoscopic or other endoscopic use is desired, remove the existing applicator tip from the SURGICEL® Powder device, and replace with the SURGICEL™ Endoscopic Applicator tip (supplied separately). In laparoscopic or other endoscopic procedures, SURGICEL® Powder should only be applied using the SURGICEL™ Endoscopic Applicator. Consult the SURGICEL™ Endoscopic Applicator Instructions for Use (IFU) for proper assembly and directions for use with the SURGICEL® Powder device.
- The SURGICEL Endoscopic Applicator is supplied with a flexible inner tip inside a rigid cannula. The rigid cannula cannot be used independently.
- The SURGICEL Endoscopic Applicator should only be used by persons having adequate training and familiarity with endoscopic techniques. Consult medical literature relative to techniques, complications, and hazards prior to performance of any endoscopic procedure.
- To prevent inadvertent device spillage, or unintended contact with tissue, organs, or blood, maintain visualization of the SURGICEL™ Endoscopic Applicator tip at all times.
- Do not compress or excessively bend the flexible inner tip of the SURGICEL Endoscopic Applicator which could obstruct the application of the powder. It is possible that the powder accumulated in the applicator could disperse beyond the target bleeding site upon compression of the bellows, which may require additional irrigation and aspiration.

ADVERSE EVENTS

- Paralysis and nerve damage have been reported when other SURGICEL® products were used around, in, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm. Blindness has been reported in connection with surgical repair of a lacerated left frontal lobe when other SURGICEL® products were placed in the anterior cranial fossa (see WARNINGS and PRECAUTIONS).
- Foreign body reactions have been reported with other products from the SURGICEL® Family of Absorbable Hemostats.
- Burning has been reported when other SURGICEL® products were applied after nasal polyp removal. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL® product was applied on surface wounds (varicose lcerations, dermabrasions, and donor sites) have also been reported.
- For more information and technical questions, call 1-800-795-0012. For complete information including indications, contraindications, warnings, precautions, adverse reactions, and directions for use, consult the product package insert.

071582-190227

SURGICEL Essential Product Information

INDICATIONS

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. SURGICEL® ORIGINAL, SURGICEL® FIBRILLAR™, SURGICEL® NU-KNIT®, and SURGICEL® SNoW™ Absorbable Hemostats can be cut to size for use in endoscopic procedures.

PRECAUTIONS

- Use only as much SURGICEL® Absorbable Hemostat as is necessary for hemostasis, holding it firmly in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction, such as encapsulation of the product, which may mimic artifacts on radiographic images, resulting in diagnostic errors and possible reoperation.
- In urological procedures, minimal amounts of SURGICEL® Absorbable Hemostat should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.
- Since absorption of SURGICEL® Absorbable Hemostat could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.
- If SURGICEL® Absorbable Hemostat is used temporarily to line the cavity of large open wounds, it should be placed so as not to overlap the skin edges. It should also be removed from open wounds by forceps or by irrigation with sterile water or saline solution after bleeding has stopped.
- Precautions should be taken in otorhinolaryngologic surgery to assure that none of the material is aspirated by the patient. (Examples: controlling hemorrhage after tonsillectomy and controlling epistaxis.)
- Care should be taken not to apply SURGICEL® Absorbable Hemostat too tightly when it is used as a wrap during vascular surgery (see Adverse Reactions section of the complete product package insert).

ADVERSE EVENTS

- "Encapsulation" of fluid and foreign body reactions have been reported.
- There have been reports of stenotic effect when SURGICEL® Absorbable Hemostat has been applied as a wrap during vascular surgery.
- Paralysis and nerve damage have been reported when SURGICEL® Absorbable Hemostat was used around, in, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm.
- Blindness has been reported in connection with surgical repair of a lacerated left frontal lobe when SURGICEL® Absorbable Hemostat was placed in the anterior cranial fossa.
- Possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy have been reported.

For more information, please consult your doctor or for product quality and technical questions, call 1-800-795-0012. For complete product information including indications, contraindications, warnings, precautions, and adverse reactions, please reference the individual product package inserts.

063768-200213

VISTASEAL™ Fibrin Sealant (Human) - Important Safety Information

INDICATION

VISTASEAL™ is indicated as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VISTASEAL is effective in heparinized patients.

CONTRAINDICATIONS

- Do not inject directly into the circulatory system.
- Do not use for the treatment of severe or brisk arterial bleeding.
- Do not use in patients with history of anaphylaxis or severe systemic reactions to human blood products.
- Do not use VISTASEAL for spraying unless the minimum recommended distance from the applicator tip to the bleeding site can be achieved.

WARNINGS AND PRECAUTIONS

- Thromboembolic events may occur if VISTASEAL is administered intravascularly.
- Only spray VISTASEAL if it is possible to accurately judge the distance from the spray tip to the tissue surface.
- Hypersensitivity reactions can occur.
- May carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

ADVERSE REACTIONS

The most common adverse reactions (reported in >1% of clinical trial subjects) were nausea and procedural pain.

For complete indications, contraindications, warnings, precautions, and adverse reactions, please reference full package insert. 115517-190529

SURGIFLO® Hemostatic Matrix Kit Essential Product Information (Made from Absorbable Gelatin Sponge, USP) with Thrombin

DESCRIPTION

SURGIFLO® with Thrombin (SURGIFLO® Hemostatic Matrix Kit) is intended for hemostatic use by applying to a bleeding surface.

ACTIONS

When used in appropriate amounts SURGIFLO® is absorbed completely within 4 to 6 weeks.

INTENDED USE/INDICATIONS

SURGIFLO®, mixed with thrombin solution, is indicated in surgical procedures (other than ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or other conventional methods is ineffective or impractical.

CONTRAINDICATIONS

- Do not use SURGIFLO® in intravascular compartments because of the risk of embolization.
- Do not use SURGIFLO® in patients with known allergies to porcine gelatin.
- Do not use SURGIFLO® 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.

WARNINGS

- SURGIFLO® should not be used in the presence of infection and should be used with caution in contaminated areas of the body.
- SURGIFLO® should not be used in instances of pumping arterial hemorrhage.
- SURGIFLO® will not act as a tampon or plug in a bleeding site.
- SURGIFLO® 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 because it may swell, resulting in nerve damage.
- Excess SURGIFLO® should be removed once hemostasis has been achieved.
- The safety and effectiveness of SURGIFLO® for use in ophthalmic procedures has not been established.
- SURGIFLO® should not be used for controlling post-partum intrauterine bleeding or menorrhagia.
- The safety and effectiveness of SURGIFLO® has not been established in children and pregnant women.
- The blue flexible applicator tip should not be trimmed to avoid exposing internal guidewire.
- The white straight applicator tip should be trimmed away from the surgical area. Cut a square angle to avoid creating a sharp tip.

PRECAUTIONS

- 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 neurosurgery has not been proven through randomized, controlled clinical studies in the United States.
- SURGIFLO® is supplied as a sterile product and cannot be resterilized.
- SURGIFLO® should not be used for packing unless excess product that is not needed to maintain hemostasis is removed. SURGIFLO® may swell up to 20% upon contact with additional fluid.
- SURGIFLO® should not be used in conjunction with autologous blood salvage circuits.
- SURGIFLO® should not be used in conjunction with methylmethacrylate adhesives.
- In urological procedures, SURGIFLO® 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. 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, has 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 has 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. 063756-161128

EVARREST® Fibrin Sealant Patch - Important Safety Information

INDICATIONS AND USAGE

EVARREST® is a fibrin sealant patch indicated for use with manual compression as an adjunct to hemostasis in adult patients undergoing surgery, when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

LIMITATIONS FOR USE

- Cannot be used in place of sutures or other forms of mechanical ligation in the treatment of major arterial or venous bleeding.
- Not for use in children under one month of age
- Laparoscopic and other minimally invasive surgeries where manual compression would be difficult to achieve.

IMPORTANT SAFETY INFORMATION

- For topical use only. Apply immediate manual compression over the entire surface of the patch and maintain contact pressure for 3 minutes to control the bleeding.
- Do not apply intravascularly. This can result in life threatening thromboembolic events.
- Do not use to treat bleeding from large defects in arteries or veins where the injured vascular wall requires conventional surgical repair and maintenance of vessel patency or where there would be persistent exposure of EVARREST® to blood flow and/or pressure during absorption of the product. Thrombosis can occur if absorbed systemically.
- Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products. EVARREST® can cause hypersensitivity reactions including anaphylaxis.
- Avoid application to contaminated areas of the body or in the presence of active infection. Infection can occur.
- EVARREST contains oxidized regenerated cellulose which adheres to bleeding surfaces. Inadvertent adhesions can occur.
- Avoid use in, around, or in proximity to, foramina in bone or areas of bony confines where swelling may cause compression.
- Use the least number of patches required to cover the entire bleeding area. Portions of excess patch material can become dislodged and migrate to other areas of the body.
- Do not use more than eight 2x4 inch (5.1 x 10.2 cm) or more than four 4x4 inch (10.2 x 10.2 cm) patches.
- Use in patients who have been previously exposed to EVARREST® has not been studied.
- May carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
- The adverse reactions reported during clinical trials occurred in less than 1% of all cases and included deep venous thrombosis, pulmonary embolism, blood fibrinogen increase, anastomotic hemorrhage, post procedural and intra-abdominal hemorrhage, abdominal distension, anemia, gastrointestinal hemorrhage, thoracic cavity drainage, pleural effusion, abdominal abscess, ascites, localized intra-abdominal fluid collection, cardiac failure, operative hemorrhage, and ischemic bowel.
- Pediatrics: Safety and effectiveness in pediatric patients have not been established. Use in children under the age of one month may be unsafe or ineffective due to small size and limited ability to apply the patch as recommended.

Please see package insert for EVARREST® Full Prescribing Information.

To report SUSPECTED ADVERSE REACTIONS, contact ETHICON Customer Support Center at 1-877-384-4266 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. 030813-171115

EVITHROM® Thrombin, Topical (Human) for Topical Use Only Lyophilized Powder for Solution

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.
- Apply EVITHROM® on the surface of bleeding tissue only.
- 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.
- 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. Hypersensitivity reactions, including anaphylaxis, may occur.
- There is a potential risk of thrombosis if absorbed systemically.
- 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.
- 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.
- None of the patients treated with EVITHROM developed antibodies to human thrombin or to human Factor V/Va. The clinical significance of these findings is unknown.

For complete indications, contraindications, warnings, precautions, and adverse reactions, please reference full package insert. 021328-180430

SURGICEL®

SNoW™
ABSORBABLE HEMOSTAT

ABSORBABLE HEMOSTAT (oxidized regenerated cellulose)

HÉMOSTATIQUE RÉSORBABLE (cellulose oxydée régénérée)

HEMOSTÁTICO ABSORVÍVEL (celulose regenerada oxidada)

HEMOSTÁTICO ABSORBIBLE (celulosa regenerada oxidada)

可吸收止血纱（氧化再生纤维素）

可吸收性止血氧化纖維（氧化再生纖維素）

ETHICON®

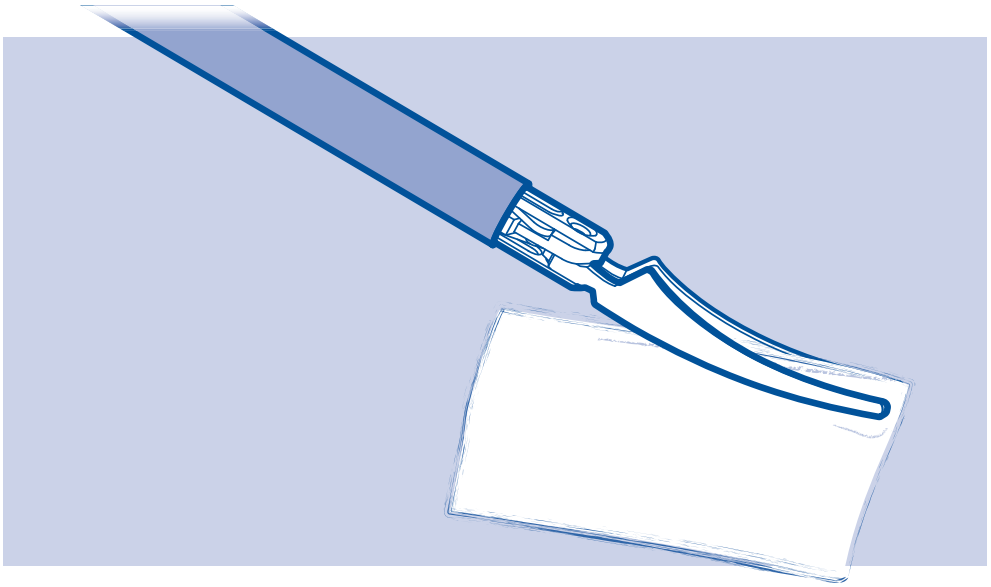

Figure 1

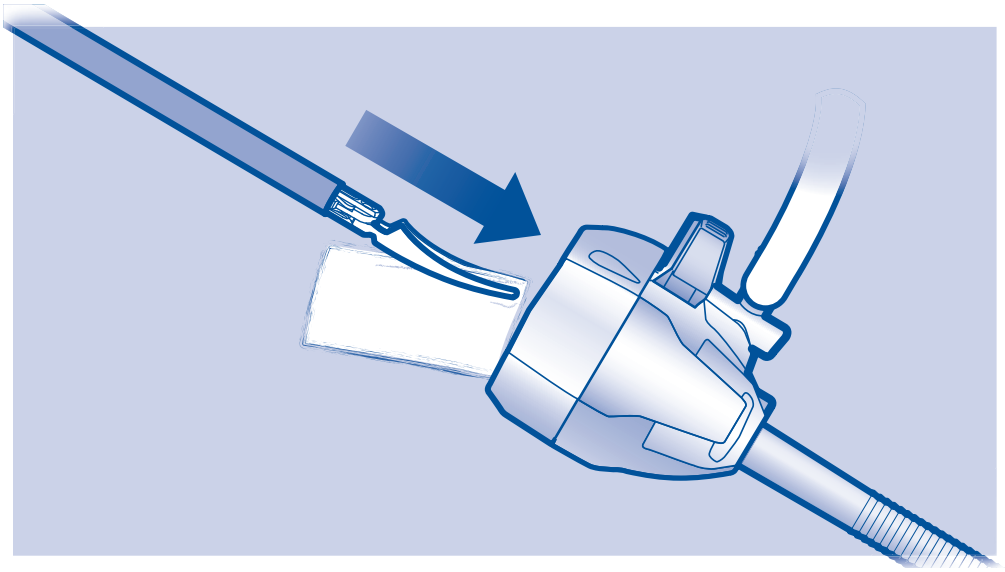

Figure 2A

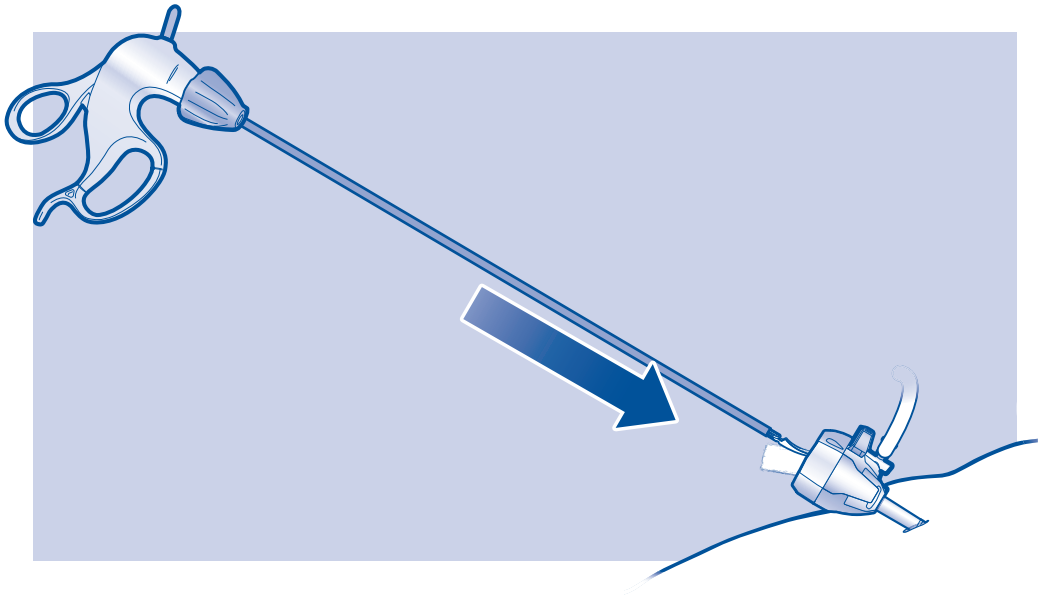

Figure 2B

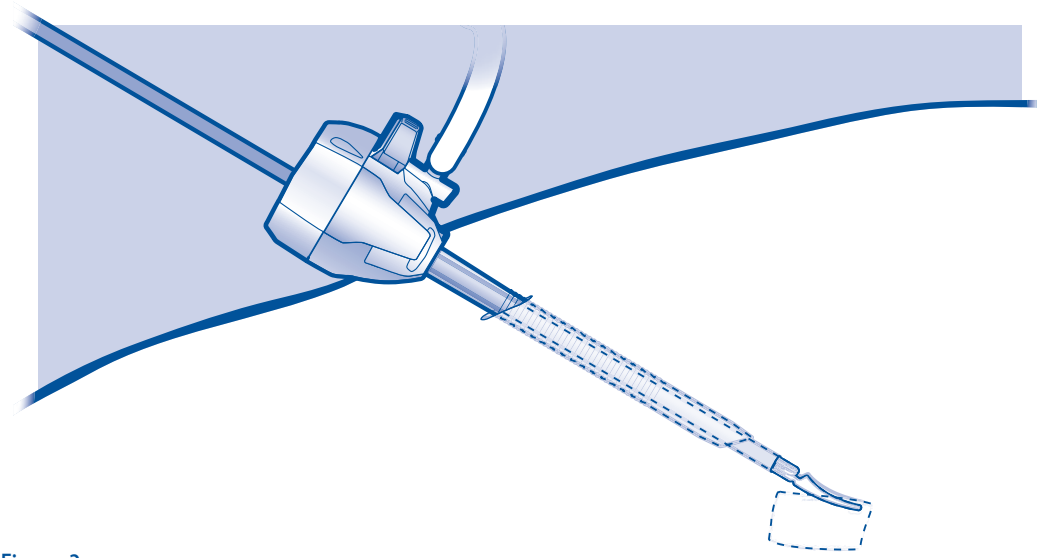

Figure 3

SURGICEL® SNoW™ Absorbable Hemostat
(oxidized regenerated cellulose)
FOR SURGICAL USE
(For dental application of this product, reference should be made to the dental use section of this insert.)

DESCRIPTION

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is a sterile absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and should be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance. The SURGICEL® SNoW™ form of the product is a Structured Non-Woven fabric. SURGICEL® SNoW™ may be more convenient than other forms of SURGICEL® for endoscopic use due to the Structured Non-Woven fabric.

ACTIONS

The mechanism of action whereby SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL® Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL® Absorbable Hemostat is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors including the amount used, degree of saturation with blood, and the tissue bed.

In addition to its local hemostatic properties, SURGICEL® Absorbable Hemostat is bactericidal *in vitro* against a wide range of gram positive and gram negative organisms including aerobes and anaerobes. SURGICEL® Absorbable Hemostat is bactericidal *in vitro* against strains of species including those of:

methicillin-resistant Staphylococcus aureus (MRSA)
penicillin-resistant Streptococcus pneumoniae (PRSP)
vancomycin-resistant Enterococcus (VRE)
methicillin-resistant Staphylococcus epidermidis (MRSE)
Staphylococcus aureus
Staphylococcus epidermidis
Micrococcus luteus
Streptococcus pyogenes Group A
Streptococcus agalactiae Group B
Streptococcus salivarius
Branhamella catarrhalis
Escherichia coli
Klebsiella pneumoniae
Lactobacillus sp.
Salmonella enteritidis
Shigella sonnei
Serratia marcescens
Bacillus subtilis
Proteus vulgaris
Corynebacterium xerosis
Mycobacterium phlei
Clostridium tetani
Clostridium perfringens
Bacteroides fragilis
Enterobacter cloacae
Pseudomonas aeruginosa
Pseudomonas stutzeri
Proteus mirabilis

Studies conducted in animals show that SURGICEL® Absorbable Hemostat in contrast to other hemostatic agents does not enhance experimental infection. (1-4) The clinical benefit of these bactericidal claims has not been studied or demonstrated.

INDICATIONS

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. SURGICEL® SNoW™ Absorbable Hemostat can be cut to size for use in endoscopic procedures.

CONTRAINDICATIONS

Although packing or wadding sometimes is medically necessary, SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) should not be used in this manner, unless it is to be removed after hemostasis is achieved (see WARNINGS and PRECAUTIONS).

SURGICEL® Absorbable Hemostat should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

When SURGICEL® Absorbable Hemostat is used to help achieve hemostasis in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, or the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure.

SURGICEL® Absorbable Hemostat should not be used to control hemorrhage from large arteries.

SURGICEL® Absorbable Hemostat should not be used on non-hemorrhagic serous oozing surfaces, since body fluids other than whole blood, such as serum, do not react with SURGICEL® Absorbable Hemostat to produce satisfactory hemostatic effect.

SURGICEL® Absorbable Hemostat is an absorbable hemostat, and should not be used as an adhesion prevention product.

WARNINGS

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is supplied sterile and as the material is not compatible with autoclaving or ethylene oxide sterilization, SURGICEL® Absorbable Hemostat should not be resterilized.

SURGICEL® Absorbable Hemostat is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

Closing SURGICEL® Absorbable Hemostat in a contaminated wound may lead to complications and should be avoided.

The hemostatic effect of SURGICEL® Absorbable Hemostat is greater when it is applied dry; therefore, it should not be moistened with water or saline.

SURGICEL® Absorbable Hemostat should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL® Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved. It must **always** 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, and in proximity to tubular structures that could become constricted by swelling, regardless of the type of surgical procedure because SURGICEL® Absorbable Hemostat, by swelling, may exert pressure resulting in paralysis and/or nerve damage. Dislodgement of SURGICEL® Absorbable Hemostat could possibly occur by means such as repacking, further intraoperative manipulation, lavage, exaggerated respiration, etc. There have been reports that in procedures such as lobectomy, laminectomy, and repair of a frontal skull fracture and lacerated lobe that SURGICEL® Absorbable Hemostat, when left in the patient after closure, migrated from the site of application into foramina in bone around the spinal cord resulting in paralysis and, in another case, the left orbit of the eye causing blindness. While

these reports cannot be confirmed, special care must be taken by physicians, ***regardless of the type of surgical procedure,*** to consider the advisability of removing SURGICEL® Absorbable Hemostat after hemostasis is achieved.

Although SURGICEL® Absorbable Hemostat is bactericidal against a wide range of pathogenic microorganisms, it is not intended as a substitute for systemically administered therapeutic or prophylactic antimicrobial agents to control or prevent postoperative infections.

PRECAUTIONS

Use only as much SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) as is necessary for hemostasis, holding it firmly in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction, such as encapsulation of the product, which may mimic artifacts on radiographic images, resulting in diagnostic errors and possible reoperation.

In urological procedures, minimal amounts of SURGICEL® Absorbable Hemostat should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.

Since absorption of SURGICEL® Absorbable Hemostat could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.

If SURGICEL® Absorbable Hemostat is used temporarily to line the cavity of large open wounds, it should be placed so as not to overlap the skin edges. It should also be removed from open wounds by forceps or by irrigation with sterile water or saline solution after bleeding has stopped.

Precautions should be taken in otorhinolaryngologic surgery to assure that none of the material is aspirated by the patient. (Examples: controlling hemorrhage after tonsillectomy and controlling epistaxis.)

Care should be taken not to apply SURGICEL® Absorbable Hemostat too tightly when it is used as a wrap during vascular surgery (see ADVERSE REACTIONS).

Endoscopic procedures should be performed only by persons having adequate training and familiarity with endoscopic techniques. Consult medical literature relative to techniques, complications, and hazards prior to performance of any endoscopic procedure.

A thorough understanding of the principles and techniques involved in laparoscopic laser and electrosurgical procedures is essential to avoid shock and burn hazards to both patient and medical personnel, and damage to the device or other medical instruments. Refer to appropriate electrosurgical system users manual for use indications and instructions to ensure that all safety precautions are followed. When endoscopic instruments and accessories from different manufacturers are employed together during a procedure, verify their compatibility prior to initiation of the procedure and ensure that isolation or grounding is not compromised.

ADVERSE REACTIONS

"Encapsulation" of fluid and foreign body reactions have been reported.

There have been reports of stenotic effect when SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) has been applied as a wrap during vascular surgery. Although it has not been established that the stenosis was directly related to the use of SURGICEL® Absorbable Hemostat, it is important to be cautious and avoid applying the material tightly as a wrapping.

Paralysis and nerve damage have been reported when SURGICEL® Absorbable Hemostat was used around, in, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm. While most of these reports have been in connection with laminectomy, reports of paralysis have also been received in connection with other procedures. Blindness has been reported in connection with surgical repair of a lacerated left frontal lobe when SURGICEL® Absorbable Hemostat was placed in the anterior cranial fossa (5) (see WARNINGS and PRECAUTIONS).

Possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy have been reported. There has been one report of a blocked ureter after kidney resection, in which postoperative catheterization was required.

Occasional reports of "burning" and "stinging" sensations and sneezing when SURGICEL® Absorbable Hemostat has been used as packing in epistaxis are believed due to the low pH of the product.

Burning has been reported when SURGICEL® Absorbable Hemostat was applied after nasal polyp removal and after hemorrhoidectomy. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL® Absorbable Hemostat was applied on surface wounds (varicose ulcerations, dermabrasions, and donor sites) also have been reported.

DOSAGE AND ADMINISTRATION

Sterile technique should be observed in removing SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) from its sterile container. Minimal amounts of SURGICEL® Absorbable Hemostat in appropriate size are laid on the bleeding site or held firmly against the tissues until hemostasis is obtained.

Opened, unused SURGICEL® Absorbable Hemostat should be discarded, because it cannot be resterilized.

HOW SUPPLIED

Sterile SURGICEL® SNoW™ Absorbable Hemostat (oxidized regenerated cellulose) is supplied as Structured Non-Woven fabric.
Code No. 2081 1 in x 2 in (2.5 cm x 5.1 cm)
Code No. 2082 2 in x 4 in (5.1 cm x 10.2 cm)
Code No. 2083 4 in x 4 in (10.2 cm x 10.2 cm)

STORAGE

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION

United States Federal law restricts this device to sale by or on the order of a physician.

CLINICAL STUDIES

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) has been found useful in helping to control capillary or venous bleeding in a variety of surgical applications, including abdominal, thoracic, neurosurgical, and orthopedic, as well as in otorhinolaryngologic procedures. Examples include gallbladder surgery, partial hepatectomy, hemorrhoidectomy, resections or injuries of the pancreas, spleen, kidney, prostate, bowel, breast or thyroid, and in amputations. (6,8)

SURGICEL® Absorbable Hemostat has been applied as a surface dressing on donor sites and superficial open wounds, controlling bleeding adequately and causing no delay in healing or interference with epithelization. (9,11) It also has been applied after dermabrasion, punch biopsy, excision biopsy, curettage, finger and toenail removal, and to traumatic wounds. In the foregoing applications, bleeding was controlled and the SURGICEL® Absorbable Hemostat was absorbed from the sites where it was applied. (10)

In cardiovascular surgery, investigators have found SURGICEL® Absorbable Hemostat useful in helping to control bleeding from implanted textile grafts, including those of the abdominal aorta. (7,12) Such grafts may leak or weep considerably, even when preclotted, but this seepage can be controlled by covering the graft with a layer or two of SURGICEL® Absorbable Hemostat after the graft is in place and before releasing the proximal and distal clamps. When the flow has been reestablished and all the bleeding controlled, the fabric either can be removed or left *in situ,* since absorption of SURGICEL® Absorbable Hemostat has been shown to occur without constriction of the graft or other untoward incident when proper wrapping technique is employed.

Otorhinolaryngologic experience with SURGICEL® Absorbable Hemostat includes adjunctive use in controlling bleeding resulting from epistaxis, tonsillectomy, adenoidectomy, removal of nasal polyps, repair of deviated septum, tympanoplasty, Stapes surgery, surgery for sinusitis, and removal of tumors. (13,14)

SURGICEL® Absorbable Hemostat has been reported useful as a hemostatic adjunct in such gynecologic procedures as oophorectomy, hysterectomy, conization of the cervix, and repair of cystorectocele. (6,15)

ANIMAL PHARMACOLOGY

The effects of SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose), absorbable gelatin sponge, and microfibrillar collagen hemostat were compared in a standardized infection model consisting of intra-abdominal and intrahepatic abscesses in mice.

This infection mimics the common characteristics of human infection with nonspore-forming anaerobic bacteria, including a chronic and progressive course. SURGICEL® Absorbable Hemostat did not increase the infectivity of normally subinfectious inocula of mixed anaerobic species in mice. With the other hemostatic agents, microfibrillar collagen hemostat and absorbable gelatin sponge, an enhancement of infectivity of anaerobic mixtures has been shown. SURGICEL® Absorbable Hemostat, in contrast to these hemostatic agents, did not enhance or provide a site for bacterial growth.

It was also found that aerobic pathogens did not grow in the presence of SURGICEL® Absorbable Hemostat. In these studies (1), SURGICEL® Absorbable Hemostat was placed in contaminated incisions of guinea pigs and markedly reduced bacterial growth of three different strains of common pathogens. In a dog model (2), it was shown that bacterial contamination of implanted Teflon™ patches in the aorta could be reduced by wrapping the area of the patch with SURGICEL® Absorbable Hemostat prior to pathogen challenge. Also, in another study (3), SURGICEL® Absorbable Hemostat and a gelatin sponge were placed in two splenotomy sites in large mongrel dogs and the animals were then challenged intravenously and the number of organisms from the splenotomy sites were measured over a period of time. The number of organisms at the site of SURGICEL® Absorbable Hemostat were significantly lower than those in the control or the absorbable gelatin sponge site.

DIRECTIONS FOR USING SURGICEL® SNoW™ ABSORBABLE HEMOSTAT IN ENDOSCOPIC PROCEDURES (see Figures 1–3):

Figure 1. SURGICEL® SNoW™ Absorbable Hemostat (oxidized regenerated cellulose) *should be cut to the appropriate size for endoscopic placement. Standard endoscopic procedures should be used up to the point of placement of the absorbable hemostat. Grasp the* SURGICEL® SNoW™ Absorbable Hemostat *at one corner.*

Figure 2A and 2B. Slowly push the grasping instrument and material into the cavity.

Figure 3. With the use of grasping instruments in a second and/or third auxiliary site, placement can be made and the material repositioned as needed.

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SURGICEL® SNoW™ Absorbable Hemostat
(oxidized regenerated cellulose)
For Dental Use
(For surgical applications of this product, reference should be made to the surgical use section of this insert.)

DESCRIPTION
SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is an absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and can be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance. The SURGICEL® SNoW™ form of the product is a Structured Non-Woven fabric. SURGICEL® SNoW™ may be more convenient than other forms of SURGICEL® for endoscopic use due to the Structured Non-Woven fabric.

ACTIONS
The mechanism of action whereby SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) accelerates clotting is not completely understood but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL® Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL® Absorbable Hemostat is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors, including the amount used, degree of saturation with blood, and the tissue bed.

INDICATIONS
SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is indicated for adjunctive use to assist in the control of bleeding in exodontia and oral surgery. It may also be used to help achieve hemostasis after single or multiple tooth extractions, alveoloplasty, gingival hemorrhage, impactions, biopsies, and other procedures in the oral cavity.

CONTRAINDICATIONS
Although packing or wadding sometimes is medically necessary, SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) should not be used in this manner unless it is to be removed after hemostasis is achieved.

SURGICEL® Absorbable Hemostat should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

WARNINGS
SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is supplied sterile and should not be autoclaved because autoclaving causes physical breakdown of the product.

SURGICEL® Absorbable Hemostat is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

Closing SURGICEL® Absorbable Hemostat in a contaminated wound may lead to complications and should be avoided.

The hemostatic effect of SURGICEL® Absorbable Hemostat is greater when it is applied dry; therefore, it should not be moistened with water or saline.

SURGICEL® Absorbable Hemostat should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL® Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved.

PRECAUTIONS

Use only as much SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) as is necessary for hemostasis, holding it in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction, such as encapsulation of the product, which may mimic artifacts on radiographic images, resulting in diagnostic errors and possible reoperation. SURGICEL® Absorbable Hemostat should be applied loosely against the bleeding surface. Wadding or packing should be avoided, especially within rigid cavities where swelling may interfere with normal function or possibly necrosis. Precautions should be taken to assure that none of the material is aspirated by the patient.

ADVERSE REACTIONS

Encapsulation of fluid and foreign body reactions have been reported.

DOSAGE AND ADMINISTRATION

Sterile technique should be observed in removing SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) from its envelope. Minimal amounts of SURGICEL® Absorbable Hemostat of appropriate size are laid on the bleeding site or held firmly against the tissues until hemostasis is obtained.

Opened, unused SURGICEL® Absorbable Hemostat should be discarded because it cannot be resterilized.

DO NOT USE IF PACK IS DAMAGED/OPENED. DO NOT RESTERILIZE/REUSE. THE USE BY DATE OF THIS PRODUCT IS PRINTED ON THE PACKAGING.

U.S. customers: to order product
call 1-800-255-2500.
For product quality and technical questions
call 1-877-384-4266.

ETHICON, LLC
San Lorenzo, Puerto Rico 00754

Made in U.S.A.

389902R04 LAB0012935v5

SURGICEL® ORIGINAL, SURGICEL® NU-KNIT® and SURGICEL® FIBRILLAR™ Absorbable Hemostats (oxidized regenerated cellulose) FOR SURGICAL USE
(For dental application of this product, reference should be made to the dental use section of this insert.)

DESCRIPTION

SURGICEL® Absorbable Hemostat is a sterile absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and should be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance. The SURGICEL® FIBRILLAR™ form of the product allows the surgeon to grasp with forceps any amount of SURGICEL® FIBRILLAR™ Hemostat needed to achieve hemostasis at a particular bleeding site. The SURGICEL® FIBRILLAR™ form may be more convenient than the knitted form for hard to reach or irregularly shaped bleeding sites. Although it is easy to pull the desired amount of SURGICEL® FIBRILLAR™ Hemostat from the entire supply, the group of selected fibers continue to cohere to one another and application to the bleeding site is easily controlled. Unwanted dispersal over the operative site does not occur.

ACTIONS

The mechanism of action whereby SURGICEL® Absorbable Hemostat accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL® Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL® Absorbable Hemostat is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors including the amount used, degree of saturation with blood, and the tissue bed.

In addition to its local hemostatic properties, SURGICEL® Absorbable Hemostat is bactericidal *in vitro* against a wide range of gram positive and gram negative organisms including aerobes and anaerobes. SURGICEL® Absorbable Hemostat is bactericidal *in vitro* against strains of species including those of:

methicillin-resistant Staphylococcus aureus (MRSA)
penicillin-resistant Streptococcus pneumoniae (PRSP)
vancomycin-resistant Enterococcus (VRE)
methicillin-resistant Staphylococcus epidermidis (MRSE)

Staphylococcus aureus
Staphylococcus epidermidis
Micrococcus luteus
Streptococcus pyogenes Group A
Streptococcus pyogenes Group B
Streptococcus salivarius
Branhamella catarrhalis
Escherichia coli
Klebsiella aerogenes
Lactobacillus sp.
Salmonella enteritidis
Shigella dysenteriae
Serratia marcescens
Bacillus subtilis
Proteus vulgaris
Corynebacterium xerosis
Mycobacterium phlei
Clostridium tetani
Clostridium perfringens
Bacteroides fragilis
Enterococcus
Enterobacter cloacae
Pseudomonas aeruginosa
Pseudomonas stutzeri
Proteus mirabilis

Studies conducted in animals show that SURGICEL® Absorbable Hemostat in contrast to other hemostatic agents does not enhance experimental infection. (1-4)

INDICATIONS

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. SURGICEL® ORIGINAL, SURGICEL® FIBRILLAR™ and SURGICEL® NU-KNIT® Hemostats can be cut to size for use in endoscopic procedures.

CONTRAINDICATIONS

Although packing or wadding sometimes is medically necessary, SURGICEL® Absorbable Hemostat should not be used in this manner, unless it is to be removed after hemostasis is achieved (See WARNINGS and PRECAUTIONS).

SURGICEL® Absorbable Hemostat should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

When SURGICEL® Absorbable Hemostat is used to help achieve hemostasis in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, or the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure.

SURGICEL® Absorbable Hemostat should not be used to control hemorrhage from large arteries.

SURGICEL® Absorbable Hemostat should not be used on non-hemorrhagic serous oozing surfaces, since body fluids other than whole blood, such as serum, do not react with SURGICEL® Absorbable Hemostat to produce satisfactory hemostatic effect.

SURGICEL® Absorbable Hemostat is an absorbable hemostat, and should not be used as an adhesion prevention product.

WARNINGS

SURGICEL® Absorbable Hemostat is supplied sterile and as the material is not compatible with autoclaving or ethylene oxide sterilization, SURGICEL® Absorbable Hemostat should not be resterilized.

SURGICEL® Absorbable Hemostat is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

Closing SURGICEL® Absorbable Hemostat in a contaminated wound may lead to complications and should be avoided.

The hemostatic effect of SURGICEL® Absorbable Hemostat is greater when it is applied dry; therefore it should not be moistened with water or saline.

SURGICEL® Absorbable Hemostat should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL® Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved. It must **always** 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, and in proximity to tubular structures that could become constricted by swelling, regardless of the type of surgical procedure because SURGICEL® Hemostat, by swelling, may exert pressure resulting in paralysis and/or nerve damage. Dislodgement of SURGICEL® Absorbable Hemostat could possibly occur by means such as repacking, further intraoperative manipulation, lavage, exaggerated respiration, etc. There have been reports that in procedures such as lobectomy, laminectomy and repair of a frontal skull fracture and lacerated lobe that SURGICEL® Absorbable Hemostat, when left in the patient after closure, migrated from the site of application into foramina in bone around the spinal cord resulting in paralysis and, in another case, the left orbit of the eye, causing blindness. While these reports cannot be confirmed, special care must be taken by physicians, ***regardless of the type of surgical procedure,*** to consider the advisability of removing SURGICEL® Absorbable Hemostat after hemostasis is achieved.

Although SURGICEL® Absorbable Hemostat is bactericidal against a wide range of pathogenic microorganisms, it is not intended as a substitute for systemically administered therapeutic or prophylactic antimicrobial agents to control or prevent post-operative infections.

PRECAUTIONS

Use only as much SURGICEL® Absorbable Hemostat as is necessary for hemostasis, holding it firmly in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction, such as encapsulation of the product, which may mimic artifacts on radiographic images, resulting in diagnostic errors and possible reoperation.

In urological procedures, minimal amounts of SURGICEL® Absorbable Hemostat should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.

Since absorption of SURGICEL® Absorbable Hemostat could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.

If SURGICEL® Absorbable Hemostat is used temporarily to line the cavity of large open wounds, it should be placed so as not to overlap the skin edges. It should also be removed from open wounds by forceps or by irrigation with sterile water or saline solution after bleeding has stopped.

Precautions should be taken in otorhinolaryngologic surgery to assure that none of the material is aspirated by the patient. (Examples: controlling hemorrhage after tonsillectomy and controlling epistaxis.)

Care should be taken not to apply SURGICEL® Absorbable Hemostat too tightly when it is used as a wrap during vascular surgery (see Adverse Reactions).

Endoscopic procedures should be performed only by persons having adequate training and familiarity with endoscopic techniques. Consult medical literature relative to techniques, complications and hazards prior to performance of any endoscopic procedure.

A thorough understanding of the principles and techniques involved in laparoscopic laser and electrosurgical procedures is essential to avoid shock and burn hazards to both patient and medical personnel and damage to the device or other medical instruments. Refer to appropriate electrosurgical system users manual for use indications and instructions to ensure that all safety precautions are followed. When endoscopic instruments and accessories from different manufacturers are employed together during a procedure, verify their compatibility prior to initiation of the procedure and ensure that isolation or grounding is not compromised.

ADVERSE REACTIONS

"Encapsulation" of fluid and foreign body reactions have been reported.

There have been reports of stenotic effect when SURGICEL® Absorbable Hemostat has been applied as a wrap during vascular surgery. Although it has not been established that the stenosis was directly related to the use of SURGICEL® Absorbable Hemostat, it is important to be cautious and avoid applying the material tightly as a wrapping.

Paralysis and nerve damage have been reported when SURGICEL® Absorbable Hemostat was used around, in, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm. While most of these reports have been in connection with laminectomy, reports of paralysis have also been received in connection with other procedures. Blindness has been reported in connection with surgical repair of a lacerated left frontal lobe when SURGICEL® Absorbable Hemostat was placed in the anterior cranial fossa (5) (See WARNINGS and PRECAUTIONS).

Possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy have been reported. There has been one report of a blocked ureter after kidney resection, in which postoperative catheterization was required.

Occasional reports of "burning" and "stinging" sensations and sneezing when SURGICEL® Absorbable Hemostat has been used as packing in epistaxis, are believed to be due to the low pH of the product.

Burning has been reported when SURGICEL® Absorbable Hemostat was applied after nasal polyp removal and after hemorrhoidectomy. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL® Absorbable Hemostat was applied on surface wounds (varicose ulcerations, dermabrasions, and donor sites) also have been reported.

DOSAGE AND ADMINISTRATION

Sterile technique should be observed in removing SURGICEL® Absorbable Hemostat from its sterile container. Minimal amounts of SURGICEL® Absorbable Hemostat in appropriate size are laid on the bleeding site or held firmly against the tissues until hemostasis is obtained.

Opened, unused SURGICEL® Absorbable Hemostat should be discarded, because it cannot be resterilized.

HOW SUPPLIED

Sterile SURGICEL® FIBRILLAR™ Absorbable Hemostat is supplied as staple fiber in envelopes of the following sizes.
Code No. 1961 1 in. x 2 in. (2.5 cm. x 5.1 cm.)
Code No. 1962 2 in. x 4 in. (5.1 cm. x 10.2 cm.)
Code No. 1963 4 in. x 4 in. (10.2 cm. x 10.2 cm.)

Sterile SURGICEL® ORIGINAL Absorbable Hemostat (oxidized regenerated cellulose) is supplied as knitted fabric strips in envelopes in the following sizes.
Code No. 1951 2 in. x 14 in. (5.1 cm. x 35.6 cm.)
Code No. 1952 4 in. x 8 in. (10.2 cm. x 20.3 cm.)
Code No. 1953 2 in. x 3 in. (5.1 cm. x 7.6 cm.)
Code No. 1955 0.5 in. x 2 in. (1.3 cm. x 5.1 cm.)

Sterile SURGICEL® NU-KNIT® Absorbable Hemostat
Code No. 1940 1 in. x 1 in. (2.5 cm. x 2.5 cm.)
Code No. 1941 1 in. x 3.5 in. (2.5 cm. x 8.9 cm.)
Code No. 1943 3 in. x 4 in. (7.6 cm. x 10.2 cm.)
Code No. 1946 6 in. x 9 in. (15.2 cm. x 22.9 cm.)

STORAGE

Store at controlled room temperature 15° - 30°C (59° - 86°F).

CAUTION

Federal law restricts this device to sale by or on the order of a physician.

CLINICAL STUDIES

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) has been found useful in helping to control capillary or venous bleeding in a variety of surgical applications, including abdominal, thoracic, neurosurgical, and orthopedic, as well as in otorhinolaryngologic procedures. Examples include gallbladder surgery, partial hepatectomy, hemorrhoidectomy, resections or injuries of the pancreas, spleen, kidney, prostate, bowel, breast or thyroid, and in amputations. (6,8)

SURGICEL® Absorbable Hemostat has been applied as a surface dressing on donor sites and superficial open wounds, controlling bleeding adequately, and causing no delay in healing or interference with epithelization. (9,11) It also has been applied after dermabrasion, punch biopsy, excision biopsy, curettage, finger and toenail removal, and to traumatic wounds. In the foregoing applications, bleeding was controlled and the SURGICEL® Absorbable Hemostat was absorbed from the sites where it was applied. (10)

In cardiovascular surgery, investigators have found SURGICEL® Absorbable Hemostat useful in helping to control bleeding from implanted textile grafts, including those of the abdominal aorta. (7,12) Such grafts may leak or weep considerably, even when pre-clotted, but this seepage can be controlled by covering the graft with a layer or two of SURGICEL® Absorbable Hemostat after the graft is in place and before releasing the proximal and distal clamps. When the flow has been reestablished and all the bleeding controlled, the fabric either can be removed or left *in situ*, since absorption of SURGICEL® Absorbable Hemostat has been shown to occur without constriction of the graft or other untoward incidents when proper wrapping technique is employed.

Otorhinolaryngologic experience with SURGICEL® Absorbable Hemostat includes adjunctive use in controlling bleeding resulting from epistaxis, tonsillectomy, adenoidectomy, removal of nasal polyps, repair of deviated septum, tympanoplasty, Stapes surgery, surgery for sinusitis, and removal of tumors. (13,14)

SURGICEL® Absorbable Hemostat has been reported useful as a hemostatic adjunct in such gynecologic procedures as oophorectomy, hysterectomy, conization of the cervix, and repair of cystorectocele. (6,15)

ANIMAL PHARMACOLOGY

The effects of SURGICEL® Absorbable Hemostat, absorbable gelatin sponge, and microfibrillar collagen hemostat were compared in a standardized infection model consisting of intra-abdominal and intrahepatic abscesses in mice.

This infection mimics the common characteristics of human infection with nonspore-forming anaerobic bacteria, including a chronic and progressive course. SURGICEL® Absorbable Hemostat did not increase the infectivity of normally subinfectious inocula of mixed anaerobic species in mice. With the other hemostatic agents, microfibrillar collagen hemostat and absorbable gelatin sponge, an enhancement of infectivity of anaerobic mixtures has been shown. SURGICEL® Absorbable Hemostat, in contrast to these hemostatic agents, did not enhance or provide a site for bacterial growth.

It was also found that aerobic pathogens did not grow in the presence of SURGICEL® Absorbable Hemostat. In these studies (1), SURGICEL® Absorbable Hemostat was placed in contaminated incisions of guinea pigs and markedly reduced bacterial growth of three different strains of common pathogens. In a dog model (2), it was shown that bacterial contamination of implanted Teflon™ patches in the aorta could be reduced by wrapping the area of the patch with SURGICEL® Absorbable Hemostat prior to pathogen challenge. Also, in another study (3), SURGICEL® Absorbable Hemostat and a gelatin sponge were placed in two splenotomy sites in large mongrel dogs and the animals were then challenged intravenously and the number of organisms from the splenotomy sites were measured over a period of time. The number of organisms at the site of SURGICEL® Absorbable Hemostat were significantly lower than those in the control, or the absorbable gelatin sponge site.

DIRECTIONS FOR USING SURGICEL® ORIGINAL, SURGICEL® NU-KNIT® AND SURGICEL® FIBRILLAR™ ABSORBABLE HEMOSTAT IN ENDOSCOPIC PROCEDURES (see Figures 1–3):

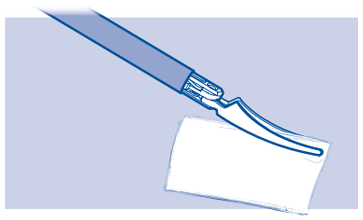

FIGURE 1

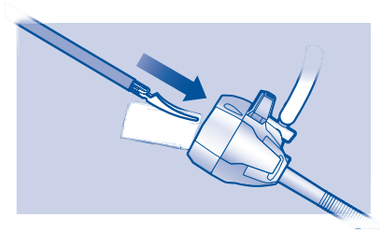

FIGURE 2A

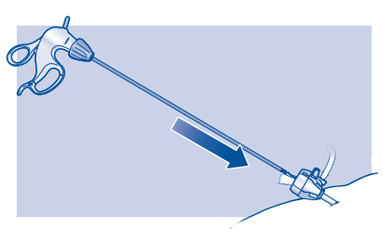

FIGURE 2B

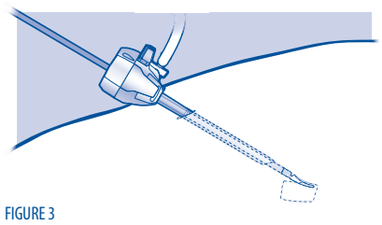

FIGURE 3

Figure 1. SURGICEL® ORIGINAL, SURGICEL® NU-KNIT® AND SURGICEL® FIBRILLAR™ Absorbable Hemostat (oxidized regenerated cellulose) *should be cut to the appropriate size for endoscopic placement. Standard endoscopic procedures should be used up to the point of placement of the absorbable hemostat. Grasp the* SURGICEL® ORIGINAL, SURGICEL® NU-KNIT® AND SURGICEL® FIBRILLAR™ Absorbable Hemostat *at one corner.*

Figure 2A and 2B. *Slowly push the grasping instrument and material into the cavity.*

Figure 3. *With the use of grasping instruments in a second and/or third auxiliary site, placement can be made and the material repositioned as needed.*

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SURGICEL® ORIGINAL, SURGICEL® NU-KNIT®, and SURGICEL® FIBRILLAR™ Absorbable Hemostats (oxidized regenerated cellulose) For Dental Use
(For surgical applications of this product, reference should be made to the surgical use section of this insert.)

DESCRIPTION

SURGICEL® Absorbable Hemostat is an absorbable knitted fabric prepared by the controlled oxidation of regenerated cellulose. The fabric is white with a pale yellow cast and has a faint, caramel-like aroma. It is strong and can be sutured or cut without fraying. It is stable and can be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance. The SURGICEL® FIBRILLAR™ form of the product allows the physician to grasp with forceps any amount of SURGICEL® FIBRILLAR™ Hemostat needed to achieve hemostasis at a particular bleeding site. The fibrillar form may be more convenient than the knitted form for hard to reach or irregularly shaped bleeding sites. Although it is easy to pull the desired amount of SURGICEL® FIBRILLAR™ Hemostat from the entire supply, the group of selected fibers continue to cohere to one another and application to the bleeding site is easily controlled. Unwanted dispersal over the operative site does not occur.

ACTIONS

The mechanism of action whereby SURGICEL® Absorbable Hemostat accelerates clotting is not completely understood but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL® Absorbable Hemostat has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL® Absorbable Hemostat is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors, including the amount used, degree of saturation with blood, and the tissue bed.

INDICATIONS

SURGICEL® Absorbable Hemostat (oxidized regenerated cellulose) is indicated for adjunctive use to assist in the control of bleeding in exodontia and oral surgery. It may also be used to help achieve hemostasis after single or multiple tooth extractions, alveoloplasty, gingival hemorrhage, impactions, biopsies, and other procedures in the oral cavity.

CONTRAINDICATIONS

Although packing or wadding sometimes is medically necessary, SURGICEL® Absorbable Hemostat should not be used in this manner unless it is to be removed after hemostasis is achieved.

SURGICEL® Absorbable Hemostat should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.

WARNINGS

SURGICEL® Absorbable Hemostat is supplied sterile and should not be autoclaved because autoclaving causes physical breakdown of the product.

SURGICEL® Absorbable Hemostat is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.

Closing SURGICEL® Absorbable Hemostat in a contaminated wound may lead to complications and should be avoided.

The hemostatic effect of SURGICEL® Absorbable Hemostat is greater when it is applied dry; therefore it should not be moistened with water or saline.

SURGICEL® Absorbable Hemostat should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.

Although SURGICEL® Absorbable Hemostat may be left *in situ* when necessary, it is advisable to remove it once hemostasis is achieved.

PRECAUTIONS

Use only as much SURGICEL® Absorbable Hemostat as is necessary for hemostasis, holding it in place until bleeding stops. Remove any excess before surgical closure in order to facilitate absorption and minimize the possibility of foreign body reaction, such as encapsulation of the product, which may mimic artifacts on radiographic images, resulting in diagnostic errors and possible reoperation. SURGICEL® Absorbable Hemostat should be applied loosely against the bleeding surface. Wadding or packing should be avoided, especially within rigid cavities, where swelling may interfere with normal function or possibly cause necrosis. Precautions should be taken to assure that none of the material is aspirated by the patient.

ADVERSE REACTIONS

Encapsulation of fluid and foreign body reactions have been reported.

DOSAGE AND ADMINISTRATION

Sterile technique should be observed in removing SURGICEL® Absorbable Hemostat from its envelope. Minimal amounts of SURGICEL® Absorbable Hemostat of appropriate size are laid on the bleeding site or held firmly against the tissues until hemostasis is obtained.

Opened, unused SURGICEL® Absorbable Hemostat should be discarded, because it cannot be resterilized.

SYMBOLS USED IN LABELING

- Do not reuse
- Do not resterilize
- Do not use if package is damaged
- Use by
- STERILE R — Sterilized using irradiation
- REF — Catalogue number
- LOT — Batch code
- Manufacturer
- CAUTION! See instructions for use
- 15°C 59°F / 30°C 86°F — Store 15-30°C (59-86°F)
- Rx only — CAUTION: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

U.S. customers: to order product,
call 1-800-255-2500;
for product quality and technical questions,
call 1-877-ETHICON.

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SURGICEL® FIBRILLAR™
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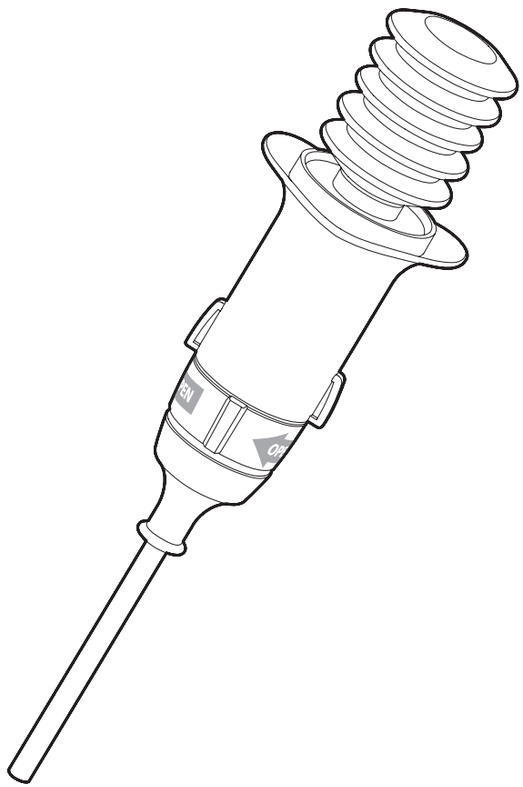
STERILE R

ETHICON®

SURGICEL® Powder

ABSORBABLE HEMOSTATIC POWDER
(oxidized regenerated cellulose)



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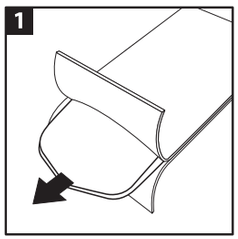

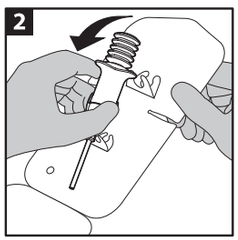

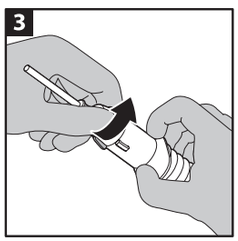

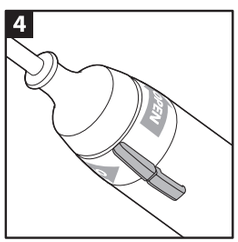

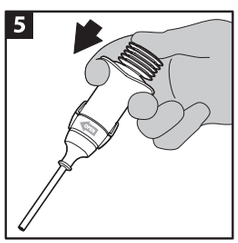

SURGICEL® Powder

en

ABSORBABLE HEMOSTATIC POWDER

(oxidized regenerated cellulose)

Do not pump device intravascularly. Life-threatening embolic events may occur if the product is applied intravascularly.

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

DESCRIPTION

SURGICEL® Powder contains Oxidized Regenerated Cellulose (ORC) prefilled in an applicator to dispense on a target bleeding site. SURGICEL® Powder is white with a pale yellow cast and has a faint, caramel-like aroma. It is stable and should be stored at controlled room temperature. A slight discoloration may occur with age, but this does not affect performance. SURGICEL® is bactericidal due to low pH characteristics against a wide range of pathogenic microorganisms.

ACTIONS

The mechanism of action whereby SURGICEL® Powder (oxidized regenerated cellulose) accelerates clotting is not completely understood, but it appears to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL® Powder has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a hemostatic adjunct in the control of local hemorrhage. When used properly in minimal amounts, SURGICEL® Powder is absorbed from the sites of implantation with practically no tissue reaction. Absorption depends upon several factors, including the amount used, degree of saturation with blood, and the tissue bed.

In addition to its local hemostatic properties, SURGICEL® Powder is bactericidal *in vitro* against a wide range of gram-positive and gram-negative organisms including aerobes and anaerobes. SURGICEL® Powder is bactericidal *in vitro* against strains of species including those of:

methicillin-resistant *Staphylococcus aureus* (MRSA)
penicillin-resistant *Streptococcus pneumoniae* (PRSP)
vancomycin-resistant *Enterococcus* (VRE)
methicillin-resistant *Staphylococcus epidermidis* (MRSE)
Staphylococcus aureus
Staphylococcus epidermidis
Micrococcus luteus
Streptococcus Group A
Streptococcus Group B
Streptococcus salivarius
Branhamella catarrhalis
Escherichia coli
Klebsiella pneumoniae
Lactobacillus sp.
Salmonella enteritidis
Shigella sonnei
Serratia marcescens
Bacillus subtilis
Proteus vulgaris
Corynebacterium xerosis
Mycobacterium phlei
Clostridium tetani
Clostridium perfringens
Bacteroides fragilis
Enterococcus sp.
Enterobacter cloacae
Pseudomonas aeruginosa
Pseudomonas stutzeri
Proteus mirabilis

INDICATIONS

SURGICEL® Powder (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. SURGICEL® Powder can also be applied in laparoscopic or other endoscopic procedures when used with the SURGICEL™ Endoscopic Applicator.

CONTRAINDICATIONS

- Do not inject or place SURGICEL® Powder into an open blood vessel. Do not use to treat bleeding from large defects in arteries or veins.
- SURGICEL® Powder should not be used to control hemorrhage from large arteries or veins.
- The SURGICEL® Powder device was not designed for intraluminal procedures.
- When SURGICEL® Powder is used to help achieve hemostasis in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, or the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure. Unlike other SURGICEL® products, SURGICEL® Powder cannot be removed from blood clots and complete removal of the device application may disrupt the clot and increase the risk of re-bleeding.
- SURGICEL® Powder should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.
- SURGICEL® Powder should not be used on non-hemorrhagic serous oozing surfaces, since body fluids other than whole blood, such as serum, do not react with SURGICEL® Powder to produce satisfactory hemostatic effect.
- SURGICEL® Powder is an absorbable hemostat, and should not be used as an adhesion prevention product.

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WARNINGS

- SURGICEL® Powder is not intended for use on dry (non-bleeding) surfaces or for prevention of bleeding.
- SURGICEL® Powder is supplied sterile and as the material is not compatible with autoclaving or ethylene oxide sterilization, SURGICEL® Powder should not be resterilized.
- SURGICEL® Powder is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.
- Closing with SURGICEL® Powder in a contaminated wound without drainage may lead to complications and should be avoided.
- The hemostatic effect of SURGICEL® Powder is greater when it is applied dry; therefore, it should not be moistened with water or saline prior to application.
- SURGICEL® Powder should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.
- Although SURGICEL® Powder may be left *in situ* when necessary, it is recommended to remove excess powder with irrigation and aspiration once hemostasis is achieved, without disturbing the clot.
- SURGICEL® Powder is dry and there may be difficulties in precise delivery under certain circumstances. Unintentional device placement may result in powder scattering and device migration that may increase the risk of adhesion formation. In preclinical *in vivo* animal studies it was demonstrated that SURGICEL® Powder does not increase the incidence of remote adhesions in laparoscopic procedures.
- Dislodgement of SURGICEL® Powder could possibly occur by intraoperative manipulation, lavage, exaggerated respiration, etc. With other SURGICEL® products there have been reports that in procedures such as lobectomy, laminectomy, and repair of a frontal skull fracture and lacerated lobe, when the product was left in the patient after closure it migrated from the site of application into foramina in bone around the spinal cord, resulting in paralysis and, in one case, the product migrated into the left orbit of the eye, causing blindness. While these reports cannot be confirmed to be related to SURGICEL® products, special care must be taken by physicians, regardless of the type of surgical procedure. Consider removing SURGICEL® Powder in these applications (procedures) after hemostasis is achieved.
- Although SURGICEL® Powder is bactericidal against a wide range of pathogenic microorganisms, it is not intended as a substitute for systemically administered therapeutic or prophylactic antimicrobial agents to control or to prevent postoperative infections.
- Do not resterilize/reuse. Reuse of this device (or portions of this device) may create a risk of product degradation, which may result in device failure and/or cross-contamination, which may lead to infection or transmission of blood-borne pathogens to patients and users.
- Do not attempt to trim the applicator tip.

PRECAUTIONS

- SURGICEL® Powder should not be used in conjunction with autologous blood salvage circuits, because its fragments may pass through the transfusion filters of blood-scavenging systems.
- Use only as much SURGICEL® Powder (oxidized regenerated cellulose) as is necessary and apply only where needed for hemostasis. Remove any excess before surgical closure in order to facilitate absorption and to minimize the possibility of foreign body reaction.
- Use minimal amount of SURGICEL® Powder required to achieve hemostasis, and remove excess powder in the area of drains to prevent clogging. In urological procedures, minimal amounts of SURGICEL® Powder should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.
- Since absorption of SURGICEL® Powder could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.
- If SURGICEL® Powder is used temporarily to line the cavity of open wounds, it should be removed by irrigation with sterile water or saline solution after bleeding has stopped.
- Precautions should be taken in otorhinolaryngologic surgery to ensure that none of the material is aspirated by the patient (e.g., controlling hemorrhage after tonsillectomy and controlling epistaxis).
- The applicator tip provided on the SURGICEL® Powder device is not intended for laparoscopic or other endoscopic use. If laparoscopic or other endoscopic use is desired, remove the existing applicator tip from the SURGICEL® Powder device, and replace with the SURGICEL™ Endoscopic Applicator tip (supplied separately). In laparoscopic or other endoscopic procedures, SURGICEL® Powder should only be applied using the SURGICEL™ Endoscopic Applicator. Consult the SURGICEL™ Endoscopic Applicator Instructions for Use (IFU) for proper assembly and directions for use with the SURGICEL® Powder device.

ADVERSE REACTIONS

Paralysis and nerve damage have been reported when other SURGICEL® products were used around, in, or in proximity to foramina in bone, areas of bony confine, the spinal cord, and/or the optic nerve and chiasm. While most of these reports have been in connection with laminectomy, reports of paralysis have also been received in connection with other procedures. Blindness has been reported in connection with surgical repair of a lacerated left frontal lobe when SURGICEL® products were placed in the anterior cranial fossa[1] (see WARNINGS and PRECAUTIONS).

Foreign body reactions have been reported with other products from the SURGICEL® Family of Absorbable Hemostats.

There have been reports with other SURGICEL® products such as possible prolongation of drainage in cholecystectomies and difficulty passing urine per urethra after prostatectomy, and blocked ureter after kidney resection, in which postoperative catheterization was required.

Burning has been reported when other SURGICEL® products were applied after nasal polyp removal and after hemorrhoidectomy. Headache, burning, stinging, and sneezing in epistaxis and other rhinological procedures, and stinging when SURGICEL® product was applied on surface wounds (varicose ulcerations, dermabrasions, and donor sites) have also been reported.[2]

DIRECTIONS FOR USE

1. Open outer foil pouch and transfer SURGICEL® Powder delivery device and inner card to sterile field (Fig. 1).
2. By holding the body of the applicator, remove SURGICEL® Powder delivery device from inner card (Fig. 2).
3. Twist to open (Figs. 3, 4).
4. SURGICEL® Powder delivery device is now ready for use. Compress bellows using light pressure to apply powder to treatment site (Fig. 5).
5. As an approximate guide, one SURGICEL® Powder delivery device can provide coverage of 33 in^2 (5.75 x 5.75 inch area) when applied in one layer at a distance of approximately 2 inches from the bleeding surface. This approximate coverage area is applicable to both open and laparoscopic use. Depending on bleeding intensity and anatomical location, more than one layer may be needed to achieve complete hemostasis at the targeted bleeding surface.
6. If necessary, powder may be held firmly against the tissues until hemostasis is obtained.
7. To prevent clogging, do not touch the tip to wet surface. Do not disassemble device bellows. Do not trim the applicator tip (see WARNINGS).
8. In the event of clogging, the tip can be wiped off using dry, sterile surgical gauze to remove clog. If clog cannot be removed using dry gauze, dispose of the clogged device and use a new SURGICEL® Powder delivery device.

DISPOSAL

Dispose of the device and packaging according to your facility's policies and procedures regarding biohazardous materials and waste.

DOSAGE AND ADMINISTRATION

Sterile technique should be observed in removing the applicator for SURGICEL® Powder (oxidized regenerated cellulose) from its sterile packaging. Apply adequate amount of SURGICEL® Powder to cover bleeding area.
Use of a non-adhering substrate to apply pressure may prevent adhesion of the formed clot to the surgical glove or other instrumentation.

Unused SURGICEL® Powder should be discarded.

HOW SUPPLIED

The applicator is provided with 3 grams of SURGICEL® Powder (oxidized regenerated cellulose) and should not be resterilized. Sterility guaranteed unless package is opened or damaged.

STORAGE

Store at controlled room temperature 15°C-30°C (59°F-86°F). Do not use after expiration date.

CLINICAL STUDIES

No clinical studies have been conducted using SURGICEL® Powder.

REFERENCES:

1. Dutton J, Tse D, Anderson R. Compressive optic neuropathy following use of intra-cranial oxidized cellulose hemostat. *Ophthalmic Surgery*. 1983;14(6):487-490.
2. Huggins S. Control of hemorrhage in otorhinolaryngologic surgery with oxidized regenerated cellulose. *Eye, Ear, Nose and Throat Monthly*. 1969;48(7).

SYMBOLS USED ON LABELING

	Do not re-use		Do not resterilize
	Do not use if package is damaged		Caution
	Use-by date		Temperature limit
	Manufacturer	REF	Catalogue number
LOT	Batch code		Caution: Federal law restricts this device to sale by or on the order of a licensed healthcare practitioner.
STERILE R	Sterilized using irradiation		

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FIBRIN SEALANT PATCH

EVARREST®

PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EVARREST® Fibrin Sealant Patch
Absorbable Patch for Topical Use
Initial US Approval: 2012

RECENT MAJOR CHANGES

Indications and Usage *(1)*	10/2016
Adverse Reactions *(6.1, 6.2)*	10/2016

INDICATIONS AND USAGE

EVARREST® is a fibrin sealant patch indicated for use with manual compression as an adjunct to hemostasis in adult patients undergoing surgery, when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. *(1)*

Limitations for Use:

- Cannot be used in place of sutures or other forms of mechanical ligation in the treatment of major arterial or venous bleeding. *(1)*
- Not for use in children under one month of age *(8.4)*
- Laparoscopic and other minimally invasive surgeries where manual compression would be difficult to achieve. *(1)*

DOSAGE AND ADMINISTRATION

For topical use only.

- Determine the number of patches to be applied based upon the surface area and anatomic location of the bleeding tissue to be treated. *(2)*
- Keep the patch dry until use. *(2.1)*
- Place the powdery (active) side of the patch on the surface of tissue. *(2.2)*
- Apply immediate manual compression over the entire surface of the patch and maintain contact pressure for 3 minutes to control the bleeding. *(2.2)*

DOSAGE FORMS AND STRENGTHS

EVARREST® Fibrin Sealant Patch consists of human fibrinogen and human thrombin embedded in a flexible composite patch component. The active side is powdery, and the non-active side has an embossed wave pattern. *(3)*

Each 2 x 4 inch (5.1 x 10.2 cm) absorbable patch contains:

- 55.5 mg per square inch (8.6 mg per square cm) human fibrinogen
- 241.9 Units per square inch (37.5 Units per square cm) human thrombin

CONTRAINDICATIONS

- Do not use to treat bleeding from large defects in arteries or veins. *(4)*
- Do not apply intravascularly. *(4)*
- Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products. *(4)*

WARNINGS AND PRECAUTIONS

- Thrombosis can occur if absorbed systemically. Apply topically to the bleeding site only. *(5.1)*
- Can cause hypersensitivity reactions including anaphylaxis. *(5.2)*
- Avoid application to contaminated areas of the body or in the presence of active infection. Infection can occur. *(5.3)*
- EVARREST® contains oxidized regenerated cellulose which adheres to bleeding surfaces. Inadvertent adhesions can occur. *(5.4)*
- Avoid use in, around, or in proximity to, foramina in bone or areas of bony confine where swelling may cause compression. *(5.5)*
- Use the least number of patches required to cover the entire bleeding area. *(5.6)*
- May carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. *(5.7)*

ADVERSE REACTIONS

The adverse reactions reported during clinical trials occurred in less than 1% of all cases and included deep venous thrombosis, pulmonary embolism, blood fibrinogen increase, anastomotic hemorrhage, post procedural and intra-abdominal hemorrhage, abdominal distension, anemia, gastrointestinal hemorrhage, thoracic cavity drainage, pleural effusion, abdominal abscess, ascites, localized intra-abdominal fluid collection, cardiac failure, operative hemorrhage, and ischemic bowel. *(6)*

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

USE IN SPECIFIC POPULATIONS

- Pediatric: Use in children under the age of one month may be unsafe or ineffective due to small size and limited ability to apply the patch as recommended. *(8.4)*

See *17* for PATIENT COUNSELING INFORMATION.

Revised 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EVARREST® is a fibrin sealant patch indicated for use with manual compression as an adjunct to hemostasis in adult patients undergoing surgery, when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

Limitations for Use:

- Cannot safely or effectively be used in place of sutures or other forms of mechanical ligation in the treatment of major arterial or venous bleeding.
- Not for use in children under one month of age
- Laparoscopic and other minimally invasive surgeries where manual compression would be difficult to achieve.

2 DOSAGE AND ADMINISTRATION

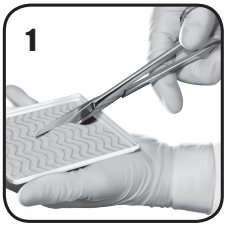
For topical use only.

- Determine the number of patches to be applied based upon the surface area and anatomic location of the bleeding to be treated.
- Do not use more than eight 2 x 4 inch (5.1 x 10.2 cm) patches.
- Use in patients who have been previously exposed to EVARREST® has not been studied.

2.1 Preparation

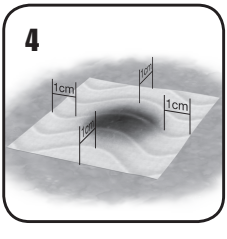
- EVARREST® comes ready to use in sterile packages and must be handled using sterile technique in aseptic conditions. Discard damaged packages as resterilization is not possible.
- To open the product, remove the foil pouch from the carton, carefully peel open the foil pouch, avoiding contact with the inside of the foil or the white sterile tray containing EVARREST.
- Remove the white sterile tray from the pouch and place onto the sterile field.
- Hold the tray securely in the palm of the hand, ensuring that the side with the holes is facing upwards, and use the tabs on the side of the tray to remove the top of the tray with the other hand.
- The lower portion of the tray contains EVARREST with the active side facing downwards. The active side is powdery in appearance. The non-active side has an embossed wave pattern.
- Keep EVARREST dry after opening. The patch can remain in the sterile field to be available for use throughout the procedure. EVARREST does not stick to gloves, forceps, or surgical instruments.

2.2 Application
Apply topically to the bleeding site only.

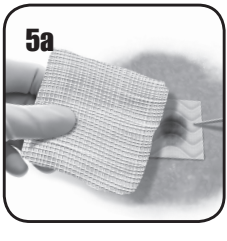


1. Using sterile scissors, carefully cut the patch to the size and shape as necessary to fit and maintain contact with the bleeding area with an overlap of approximately 0.5 to 1 inch (1 to 2 cm). Keep the powdery white-to-yellow color active side of the patch facing down while in the tray.
2. Remove excess blood or fluid from the site of application to improve visibility. Do not use on non-visualized surfaces. Do not use to treat bleeding from defects in large arteries or veins where the injured vascular wall requires conventional surgical repair for maintenance of vessel patency.

3. Apply the active side of the patch to the bleeding area. Allow full contact with the tissue or prosthetic graft. The product is activated upon contact with fluid and then adheres, conforming to tissue with continuous manual compression.

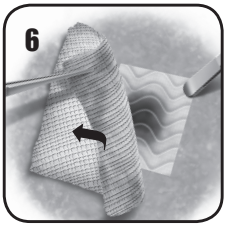


4. Apply a sufficient number of patches to adequately cover the entire bleeding area, with an overlap of approximately 0.5 to 1 inch (1 to 2 cm). Use the least number of patches to cover the bleeding area *[see Warnings and Precautions (5.6)]*.



5. (a) Hold dry or moist laparotomy pads or surgical gauze over EVARREST® to achieve full contact with the bleeding surface.

(b) To ensure hemostasis, immediately apply continuous manual compression over the entire surface of the patch (including the area of overlap) sufficient to stem all bleeding. Ensure even pressure distribution, full tissue apposition and avoid movement of the patch over the entire bleeding area. Maintain continuous manual compression for 3 minutes.



6. Gently remove laparotomy pads or surgical gauze from the application site without disrupting or dislodging EVARREST or the clot. If irrigation is necessary, use care not to dislodge the patch. Inspect the patch to ensure that it is in full contact with the treated area. If placement of the patch is unsatisfactory, remove the patch and use a new patch *[see Dosage and Administration (2)]*. Removal of the patch may disrupt the clot and result in re-bleeding.
7. Discard unused, opened patches at the end of the procedure.

2.3 Retreatment

- Retreatment may be required if there are folds, creases, or crimps in the patch. If not satisfied with the placement of the patch, or if bleeding still occurs during or after the specified duration of compression, remove the used patch and repeat the application procedure above with a new patch.
- If continued bleeding is due to insufficient coverage of the bleeding area, additional patches may be applied. Ensure that the edges overlap (by approximately 0.5 to 1 inch or 1 to 2 cm) with the existing patch.
- If continued bleeding is due to incomplete adherence to the tissue (where bleeding persists from under the dressing), remove the patch and use a new one.

3 DOSAGE FORMS AND STRENGTHS

EVARREST® Fibrin Sealant Patch consists of human fibrinogen and human thrombin embedded in a flexible composite patch component. The active side is white-to-yellow in color and powdery in appearance, and the non-active side has an embossed wave pattern.

Each 2 x 4 inch (5.1 x 10.2 cm) absorbable patch of EVARREST contains 55.5 mg per square inch (8.6 mg per square cm) of human fibrinogen and 241.9 Units[1] per square inch (37.5 Units per square cm) of human thrombin.

[1] The Thrombin 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 Organization (WHO) Second International Standard for Thrombin, 01/580. Therefore, a Unit used herein is equivalent to an International Unit.

4 CONTRAINDICATIONS

Do not use EVARREST® for

- Bleeding from large defects in visible arteries or veins where the injured vascular wall requires conventional surgical repair and maintenance of vessel patency or where there would be persistent exposure of EVARREST to blood flow and/or pressure during absorption of the product.
- Intravascular application. This can result in life-threatening thromboembolic events.
- Individuals known to have anaphylactic or severe systemic reaction to human blood products.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis

Thrombosis can occur if EVARREST® is absorbed systemically. Apply EVARREST topically to the bleeding site only.

5.2 Hypersensitivity Reactions

EVARREST® can cause hypersensitivity reactions, including anaphylactic reactions. Symptoms associated with allergic anaphylactic reactions include flush, urticaria, pruritus, nausea, drop in blood pressure, tachycardia or bradycardia, dyspnea, severe hypotension and anaphylactic shock.

5.3 Infection

Avoid application to contaminated or infected areas of the body, or in the presence of active infection. Infection can occur from application to an infected site.

5.4 Adhesions

EVARREST® contains oxidized regenerated cellulose which adheres to bleeding surfaces. Inadvertent adhesions can occur.

5.5 Compression

Avoid using EVARREST® in, around, or in proximity to, foramina in bone or areas of bony confine where swelling may cause nerve or blood vessel compression.

5.6 Dislodged Patch Material

Use the least number of patches possible during surgical procedures because portions of excess patch material can become dislodged and migrate to other areas of the body.

5.7 Transmissible Infectious Agents

Because the biological components of this product are made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmitting viral agents has been minimized 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 during the manufacturing process *[see Description (11)]*. Despite these measures, such products still potentially can transmit disease. There is also the possibility that unknown infectious agents may be present in such products.

Any infection considered by a physician to possibly have been transmitted by this product should be reported by the physician or other healthcare provider to ETHICON Customer Support Center at 1-877-384-4266.

6 ADVERSE REACTIONS

All Adverse Reactions reported during the clinical trials occurred at a frequency of less than 1%. Most adverse reactions were reported as single events: intra-abdominal hemorrhage, abdominal distension, anemia, thoracic cavity drainage, pleural effusion, abdominal abscess, ascites, deep vein thrombosis, localized intra-abdominal fluid collection, operative hemorrhage, ischemic bowel and pulmonary embolism except blood fibrinogen increased (3 events, 0.8%) anastomotic hemorrhage (3 events, 0.8%) and post procedural hemorrhage (2 events, 0.5%).

6.1 Clinical Trials Experience

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

EVARREST® was used to treat soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, or thoracic surgery, suture hole bleeding during cardiovascular surgery, and parenchymal bleeding during hepatic or renal surgery across all clinical trials involving 381 subjects treated with EVARREST and 272 control subjects. Of the enrolled subjects, 4.7% of EVARREST treated subjects (18 subjects out of 381) and 2.6% of control subjects (7 subjects out of 272) experienced one or more adverse reactions. Table 1 indicates the number of re-bleeding and thromboembolic events reported from each clinical trial.

Table 1. Re-bleeding and Thromboembolic Adverse Reactions Reported in Clinical Trials

System Organ Class	Preferred term	EVARREST® All (n=381)	Relationship to Treatment	Control (n=272)	Relationship to Treatment
Abdominal, pelvic, retroperitoneal, and non-cardiac thoracic surgery					
Injury, Poisoning and Procedural Complications	Operative Hemorrhage	1 (0.3%)	Possibly related	2 (0.7%)	Related and Possibly related
Respiratory, Thoracic and Mediastinal Disorders	Pulmonary Embolism	1 (0.3%)	Possibly related	0 (0.0%)	NA
Vascular Disorders	Deep Vein Thrombosis	1 (0.3%)	Possibly related	0 (0.0%)	NA
Liver Surgery					
Gastrointestinal Disorders	Intra-Abdominal Hemorrhage	1 (0.3%)	Possibly related	0 (0.0%)	NA
Injury, Poisoning and Procedural Complications	Post Procedural Hemorrhage	1 (0.3%)	Possibly related	0 (0.0%)	NA
Renal Surgery					
Injury, Poisoning and Procedural Complications	Post Procedural Hemorrhage	1 (0.3%)	Related	0 (0.0%)	NA
Cardiovascular Surgery					
Injury, Poisoning and Procedural Complications	Anastomotic Hemorrhage	3 (0.8%)	2 x Related; 1 x Possibly related	1 (0.4%)	Possibly related
	Post Procedural Hemorrhage	0 (0.0%)	NA	2 (0.7%)	Possibly related

A prospective, randomized, controlled single-center post-marketing safety study observing the clinical utility of EVARREST against Standard of Care (SoC) in soft tissue bleeding during intra-abdominal, retroperitoneal, pelvic and non-cardiac thoracic surgery was conducted. Standard of Care was manual compression (MC) with or without a topical absorbable hemostat (TAH) or any other adjunctive hemostasis technique that was deemed by the surgeon to be his/her standard of care. The incidence of thromboembolic events, the incidence of post-operative bleeding events specifically related to the target bleeding site and the incidence of increased blood fibrinogen levels were assessed and recorded up to the 30 days (+/- 14 days) follow-up period.

The post-marketing study enrolled 150 subjects and demographics were balanced across the treatment groups. In both groups, no adverse events were assessed as re-bleeding related to target bleeding site; events assessed as thromboembolic events were experienced by 2/75 subjects (2.7%) in the EVARREST group and 7 subjects (9.3%) in the SoC group. One (1/75) adverse reaction of deep vein thrombosis was reported in the EVARREST group. No significant differences were observed in the frequency of adverse reactions between treatment groups.

Immunogenicity was evaluated in soft tissue clinical studies by testing blood samples collected for antibodies to human thrombin and fibrinogen. Three subjects out of 145 (~2%) in the group treated with EVARREST showed an increase in the titer of anti-thrombin antibodies after treatment. Two subjects out of 145 (~1%) in the group treated with EVARREST showed a transient increase in fibrinogen antibody titers, with titer levels back at background levels 8 to 10 weeks after treatment. None of the patients in any treatment group had a significant change in antibody titer to thrombin or fibrinogen. The general antibody level in the treated population was not affected by treatment with EVARREST and resembled the normal levels in healthy subjects.

6.2 Post Marketing Safety Data

No new safety signals were identified from post-marketing experience. There were no reported adverse events that were confirmed to be related to EVARREST®. Two cases of post-operative infection were reported when EVARREST was used off-label in a contaminated area. In another two cases, lack of expected efficacy in achieving intraoperative hemostasis was reported in coagulopathic patients: however, because these were spontaneous reports, correct application of the product could not be confirmed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

There are no data with EVARREST® use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with EVARREST. It is not known whether EVARREST can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EVARREST should be applied to a pregnant woman only if clearly needed.

8.2 Lactation

Risk Summary

There is no information regarding the presence of any component of EVARREST® in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVARREST and any potential adverse effects on the breastfed infant from EVARREST or from the underlying maternal condition.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Use of EVARREST® in children under the age of one month may be unsafe or ineffective due to small size and limited ability to apply the patch as recommended. Slow absorption and possibility of adhesions can further complicate use of EVARREST in the neonates.

8.5 Geriatric Use
Clinical trials included 181 subjects of 65 years of age or older who were treated with EVARREST®. No differences in safety or efficacy were observed between the elderly and younger patients.

11 DESCRIPTION
EVARREST® Fibrin Sealant Patch is a sterile, bio-absorbable combination product, comprised of two biological components (human plasma-derived fibrinogen and thrombin) embedded in a flexible composite patch component. The active side is white-to-yellow in color and powdery in appearance; the non-active side has an embossed wave pattern.

The patch component of EVARREST consists of an oxidized regenerated cellulose (ORC) layer underlying a layer of polyglactin 910 (PG910) non-woven fibers. The PG910 layer contains the embedded biological components. The patch component provides a large surface area for the biological components and imparts inherent mechanical integrity to the product. The flexibility of EVARREST accommodates the physiological movements of tissues and organs.

Each 2 x 4 inch (5.1 x 10.2 cm) EVARREST patch contains 55.5 mg per square inch (8.6 mg per square cm) of human fibrinogen and 241.9 Units per square inch (37.5 Units per square cm) of human thrombin. Additional inactive ingredients are: arginine hydrochloride, calcium chloride, glycine, human albumin, mannitol, sodium acetate, sodium chloride, and sodium citrate. EVARREST does not contain any preservative.

EVARREST is sterilized by electron-beam irradiation after completion of inner and outer packaging resulting in a sterile product in a sterile inner package.

Viral Clearance

The biological components of EVARREST® (human fibrinogen and human thrombin) are manufactured from pooled human plasma collected in FDA-licensed facilities in the United States. Human plasma is tested by FDA-licensed Nucleic Acid Tests (NAT) for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus-1 (HIV-1). NAT testing for hepatitis A virus (HAV) and parvovirus B19 is also performed. In addition, human plasma is tested for the presence of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (anti-HCV) and human immunodeficiency viruses types 1 and 2 (anti-HIV1/2).

The manufacturing procedure for human fibrinogen and human thrombin include processing steps designed to reduce the risk of viral transmission. In particular, the virus clearance steps in the manufacture of human fibrinogen include solvent/detergent (S/D) treatment and pasteurization. The virus clearance steps in the manufacture of human thrombin include S/D treatment and nanofiltration.

The virus clearance capacity of these procedures has been validated using viruses with a range of physico-chemical characteristics. These *in vitro* validation studies were conducted using samples from manufacturing intermediates spiked with virus suspensions of known titers followed by further processing under conditions equivalent to those in the respective manufacturing steps. The results of virus clearance validation studies are summarized in Table 2 and Table 3.

Table 2. Virus Reduction Factors for Human Fibrinogen

	Reduction Factor (log_{10}) of virus tested					
	* Enveloped Viruses			† Non-Enveloped Viruses		
Manufacturing Step	**HIV-1**	**BVDV**	**PRV**	**EMCV**	**HAV**	**CPV**
SD Treatment	> 4.42	> 4.39	> 3.96	Not Tested	Not Tested	0.0
Pasteurization	> 4.39	> 5.46	6.04	3.69	> 5.78	1.33
Cumulative Virus Reduction Factor	**> 8.81**	**> 9.85**	**> 10.00**	**3.69**	**> 5.78**	**1.33**

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

Table 3. Virus Reduction Factors for Human Thrombin

	Reduction Factor (log_{10}) of virus tested						
	* Enveloped Viruses				† Non-Enveloped Viruses		
Manufacturing Step	**HIV-1**	**SBV**	**BVDV**	**PRV**	**EMCV**	**HAV**	**CPV**
SD Treatment	> 5.82	> 5.31	> 4.74	> 4.25	Not Tested	Not Tested	0.0
Nanofiltration	> 4.36	> 5.32	Not Tested	> 5.47	6.37	6.95	5.85
Cumulative Virus 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

12.1 Mechanism of Action

The mechanism of action of EVARREST® is based on the interaction between the biological components and the physiology of the fibrin clot formation. Upon contact with a bleeding wound surface, the biological components embedded in the patch component are hydrated, and the subsequent fibrinogen-thrombin reaction initiates the last step in the cascade of biochemical reactions – conversion of fibrinogen into fibrin monomers that further polymerize to form the fibrin clot.

Hemostasis is achieved when the formed fibrin clot integrates with the patch component and adheres to the wound surface thus also providing a physical barrier to bleeding.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of EVARREST® or studies to determine the effects of EVARREST on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of EVARREST was completed to demonstrate minimal carcinogenic risk from product use.

13.2 Animal Toxicology and Pharmacology

The biological components of EVARREST® are degraded by fibrinolysis and phagocytosis, similarly to endogenous fibrin. As resorption progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated. In swine and rodent models, topically applied EVARREST was absorbed at approximately 8 weeks after application with less than 10% of the initial material remaining, which further degraded exponentially over time. In a rodent repeat-dosing model study, EVARREST was subcutaneously applied on Day 0 at twenty times the clinical dose at multiple surgical sites, or on Day 0 and 14 at ten times the clinical dose within multiple surgical sites. There was evidence of resorption at the site or sites of implantation after both single and repeated applications of EVARREST at study termination 90 days later. Repeat use of EVARREST in a rodent model was not associated with any increased local or systemic toxicological effects when used in multiple sites within the same procedure or when used in two procedures conducted 2-weeks apart at separate sites.

14 CLINICAL STUDIES

14.1 Abdominal, pelvic, retroperitoneal, and non-cardiac thoracic surgery

A prospective, randomized controlled trial including 141 subjects (median age: 62 years; range 26 to 89 years) was performed to compare the safety and hemostatic effectiveness of EVARREST® with that of oxidized regenerated cellulose (ORC), an absorbable hemostat, when used as an adjunct to control bleeding after primary methods to achieve hemostasis (e.g., suture, cautery, ligature) proved ineffective or impractical during open abdominal, pelvic, retroperitoneal, and non-cardiac thoracic surgery.

A total of 90 subjects were randomized in a 2:1 ratio (60 treated with EVARREST, 30 treated with ORC). An additional 51 subjects were enrolled and treated with EVARREST during a subsequent non-randomized phase. Of the total 141 enrolled subjects, 63.1% were male; 80.1% were White/Caucasian; 18.4% were Black; 0.7% were Asian; and 0.7% were Hispanic/Latino. Median body mass index was 27 kg/m^2 (range: 17 to 53 kg/m^2). Demographic characteristics were balanced across treatment groups.

EVARREST demonstrated a statistically significant difference compared with ORC, 98.3% versus 53.3% ($p < 0.0001$) in the proportion of subjects achieving hemostatic success at 4 minutes after identification of the target bleeding site and randomization, with no re-bleeding requiring treatment during a subsequent 6-minute observation period and sustained hemostasis until fascial closure at the end of the surgery (Table 4).

Table 4. Subjects Achieving Hemostasis at 4 Minutes from Identification of the Target Bleeding Site and Randomization, with no Re-bleeding until Fascial Closure at the End of the Surgery

EVARREST®	ORC	p-value	Treatment Difference	95% Confidence Interval
59/60 (98.3%)	16/30 (53.3%)	<0.0001	45.0%	27.9%, 62.5%

Efficacy data for the 51 non-randomized subjects treated with EVARREST were supportive of the above findings, with 50/51 subjects (98.0%) achieving hemostatic success at 4 minutes after randomization. No re-bleeding requiring treatment occurred during a subsequent 6-minute observation period.

14.2 Liver Surgery

Two prospective, randomized controlled trials including a total of 206 subjects were performed to compare the safety and hemostatic effectiveness of EVARREST® with that of Standard of Care (defined as manual compression with or without a topical absorbable hemostat) when used as an adjunct to control bleeding after primary methods to achieve hemostasis (e.g., suture, cautery, ligature) proved ineffective or impractical during liver surgery.

The first study included 104 subjects (median age: 65 years; range 31 to 82 years): 58.7% of the subjects were male; 95.2% were White/Caucasian; 1.9% were Asian; and 1% were Black. Median body mass index was 27 kg/m^2 (range: 15 to 43 kg/m^2). Demographic characteristics were balanced across treatment groups.

A total of 84 subjects were randomized in a 1:1 ratio (40 randomized to EVARREST, 44 to Standard of Care). An additional 20 subjects were enrolled and treated with EVARREST during a non-randomized phase. One subject should have been randomized to EVARREST but was treated with Standard of Care. This subject was analyzed in the EVARREST group for the Intent to Treat Set.

EVARREST demonstrated a statistically significant difference compared with Standard of Care (82.5% versus 29.5%; $p < 0.0001$) in the proportion of subjects achieving hemostatic success at 4 minutes after identification of the target bleeding site and randomization, with no re-bleeding requiring treatment any time prior to initiation of wound closure (Table 5). The treatment difference between EVARREST and Standard of Care was greater in subjects with bleeding from abnormal hepatic tissue (e.g., cirrhotic or steatotic) than in subjects with normal tissue bleeding (65.2% versus 48.8%, respectively).

Table 5. Subjects Achieving Hemostasis at 4 Minutes from Identification of the Target Bleeding Site and Randomization, with no Re-bleeding until Fascial Closure at the End of the Surgery

EVARREST®	Standard of Care	p-value	Treatment Difference	95% Confidence Interval
33/40 (82.5%)	13/44 (29.5%)	<0.0001	53.0%	32.9%, 68.5%

Efficacy data for the 20 non-randomized subjects treated with EVARREST were supportive of the above findings, with 20/20 subjects (100.0%) achieving hemostatic success at 4 minutes after identification of the target bleeding site and randomization. No re-bleeding requiring treatment occurred any time prior to the initiation of wound closure.

The second study included 102 subjects (median age: 63 years; range 23 to 85 years) randomized in a 1:1 ratio (50 randomized to EVARREST, 52 to Standard of Care). Sixty-one percent of the subjects were male; 85.3% were White/Caucasian; 9.8% were Black; 2.9% were Asian; and 3% were Hispanic. Median body mass index was 27 kg/m^2 (range: 15 to 43 kg/m^2). Demographic characteristics were balanced across the treatment groups.

EVARREST demonstrated a statistically significant difference compared with Standard of Care (96% versus 46.2%; $p < 0.0001$) in the proportion of subjects achieving hemostatic success at 4 minutes after identification of the target bleeding site and randomization. No re-bleeding requiring treatment occurred at any time prior to initiation of wound closure (Table 6). The treatment difference between EVARREST and Standard of Care was shown to be greater in subjects undergoing non-anatomic resection than in subjects undergoing anatomic resection (58.1% versus 39.5%, respectively). Data from this study further support the efficacy of EVARREST as an adjunct to hemostasis in the control of bleeding in liver surgery.

Table 6. Subjects Achieving Hemostasis at 4 Minutes from Identification of the Target Bleeding Site and Randomization, with no Re-bleeding until Fascial Closure at the End of the Surgery

EVARREST®	Standard of Care	p-value	Treatment Difference	95% Confidence Interval
48/50 (96.0%)	24/52 (46.2%)	<0.0001	49.8%	34.5%, 63.5%

14.3 Cardiovascular Surgery

Two prospective, randomized controlled trials enrolling a total of 198 subjects were performed to evaluate the safety and efficacy of EVARREST® as an adjunct to control of bleeding during cardiovascular surgery in subjects undergoing major aortic reconstruction using a synthetic graft (with the exception of ePTFE grafts) while on cardiopulmonary bypass and prior to heparin reversal. The target bleeding site was located on the tissue-graft or graft-graft anastomosis.

The first study included 42 subjects randomized 1:1:1 (13 randomized to EVARREST, 18 to TachoSil®, and 11 to Standard of Care). Median age was 56 years in the EVARREST cohort, 60 years in the TachoSil® Fibrin Sealant Patch (TachoSil®) cohort and 61 years in the Standard of Care cohort (range: 28-83 years). Standard of Care was defined as manual compression with or without a topical absorbable hemostat. The number of males exceeded the number of females (69.2% EVARREST, 83.3% TachoSil® and 81.8% Standard of Care) and most were White/Caucasian (69.2% EVARREST, 61.1% TachoSil® and 54.5% Standard of Care). Other demographic characteristics were balanced across treatment cohorts. The majority of subjects had a body mass index (BMI) categorized as "overweight" (BMI: 25 – <30 kg/m^2), "obese" (BMI: 30 – <40 kg/m^2) or "morbidly obese" (BMI ≥ 40 kg/m^2). These categories combined represented 61.6% of EVARREST subjects, 61.2% of TachoSil® subjects and 63.7% of Standard of Care subjects.

Table 7 shows a significant difference in hemostasis between EVARREST and TachoSil® (92.3% *versus* 33.3%; 2.77; 95% CI 1.53, 5.74) and between EVARREST and Standard of Care (92.3% *versus* 45.5%; 2.03; 95% CI 1.18, 4.39).

Table 7. Hemostasis at 3 Minutes with No Re-bleeding Until Initiation of Final Chest Wall Closure

Treatment Comparison	Hemostatic Efficacy Rates (%)		Risk Ratio (RR)	95% CI* for RR
EVARREST® to TachoSil®	92.3% (12/13)	33.3% (6/18)	2.77	(1.53, 5.74)
EVARREST® to SoC	92.3% (12/13)	45.5% (5/11)	2.03	(1.18, 4.39)

* Using Koopman's method

The second study included 156 subjects randomized 1:1 (76 randomized to EVARREST, 80 to TachoSil®). In both treatment cohorts, there were more males than females (75% EVARREST; 75% TachoSil®). Median age was 66 years in the EVARREST cohort and 64 years in the TachoSil® cohort (range: 24-83 years). The majority of subjects were White/Caucasian (82.9% EVARREST; 81. 3% TachoSil®). Median BMI in the EVARREST cohort was 27.1 kg/m^2 (range 17.7 – 44.6 kg/m^2); 71.0% of subjects were categorized as "overweight" (BMI 25 – <30 kg/m^2), "obese" (BMI 30 – <40 kg/m^2) or "morbidly obese" (BMI ≥ 40 kg/m^2). Median BMI in the TachoSil® cohort was 27.9 kg/m^2(range 18.5 – 54.9 kg/m^2); 77.6% of subjects were categorized as "overweight", "obese" or "morbidly obese."

Table 8 shows that EVARREST was superior to TachoSil® in the proportion of subjects achieving hemostasis at the target anastomotic bleeding site at 3 minutes after treatment application and with no re-bleeding requiring treatment until chest wall closure (75.0% versus 45.0%; p = 0.0001). Data from this study support the efficacy of EVARREST as an adjunct to hemostasis in the control of bleeding in cardiovascular surgery.

Table 8. Subjects Achieving Hemostasis at 3 Minutes Following Treatment Application, With No Re-Bleeding Up Until Chest Wall Closure

EVARREST®	TachoSil®	p-value	Treatment Difference
57/76 (75.0%)	36/80 (45.0%)	0.0001	30.0%

16 HOW SUPPLIED/STORAGE AND HANDLING

EVARREST® is packaged in a polyester tray and lid assembly within an outer pouch composed of polyester laminated aluminum foil with an inner heat seal coating. The tray and lid assembly maintains product integrity during storage and transport. The aluminum foil pouch serves as a barrier to moisture and microbial contamination to maintain product sterility. Each aluminum foil pouch is contained in a labeled cardboard package.

Each individual package contains two 2 x 4 inch (5.1 x 10.2 cm) EVARREST patches (NDC 63713-050-25 per patch and NDC 63713-050-24 per package).

- Use EVARREST before the expiration date indicated on the carton.
- Store unopened packages of EVARREST at 2 to 25°C. EVARREST does not require refrigeration. Do not freeze.
- Do not use if package is opened or damaged.
- Once opened, keep EVARREST dry to avoid activation of the biological components prior to use.

17 PATIENT COUNSELING INFORMATION

- Advise patients to consult their physician if they experience chest pain, shortness of breath, difficulty speaking or swallowing, leg tenderness or swelling, or other symptoms of thromboembolism.
- Inform patients that EVARREST® may carry a risk of transmitting infectious agents, e.g., viruses such as hepatitis A and parvovirus B19 and theoretically the CJD agent. Instruct patients to consult their physician if symptoms of B19 virus infection (fever, drowsiness, and chills, followed two weeks later by a rash and joint pain) or hepatitis A (several days to weeks of poor appetite, fatigue and low-grade fever followed by nausea, vomiting and abdominal pain, dark urine, yellowed complexion) appear.

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ETHICON™

SURGIFLO® HEMOSTATIC MATRIX KIT with Thrombin

Instructions for Use

4547681

REF 2994

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SURGIFLO® Hemostatic Matrix Kit

(Made from Absorbable Gelatin Sponge, USP)

with Thrombin

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

SURGIFLO® Hemostatic Matrix Kit with Thrombin (SURGIFLO® Hemostatic Matrix Kit) is intended for hemostatic use by applying to a bleeding surface.

The Kit contains:

1. A sterile tray with *all* sterile components to prepare the Flowable Gelatin Matrix,
2. A sterile tray with *all* surface sterilized Thrombin kit components to prepare the Thrombin Solution.
    1. The Flowable Gelatin Matrix comes in a tray with *all* sterile components:
        - A sterile pre-filled blue plunger syringe containing the porcine Gelatin Matrix that is off-white in appearance,
        - A sterile empty syringe,
        - A sterile liquid transfer cup,
        - A sterile blue flexible applicator tip that is bendable in all directions, and
        - A sterile white applicator tip that can be trimmed to desired length
    2. The surface sterilized components to prepare the Thrombin Solution include:
        - A Thrombin vial, EVITHROM® Thrombin, Topical (Human), containing 2000 International Units (IU) of sterile lyophilized human thrombin powder for reconstitution,
        - A needle-free syringe containing 2 mL of Sterile Water for Injection (Sterile WFI),
        - A sterile vial adapter.

For prescribing information on the Thrombin component, please refer to the EVITHROM® Thrombin, Topical (Human) Prescribing Information on page 9.

Thrombin should be reconstituted using the vial adapter and the needle-free syringe with Sterile WFI.

The Thrombin Solution must be added to the Flowable Gelatin Matrix prior to use.

Once the hemostatic matrix is mixed with the Thrombin Solution, the appropriate applicator tip should be attached to the syringe for product delivery onto the bleeding site.

ACTIONS

SURGIFLO® Hemostatic Matrix Kit has hemostatic properties. 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 minimal.

INTENDED USE/INDICATIONS

SURGIFLO® Hemostatic Matrix, mixed with thrombin solution, is indicated in surgical procedures (other than ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or other conventional methods is ineffective or impractical.

CONTRAINDICATIONS

- 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.
- 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.

WARNINGS

- Do not inject or compress SURGIFLO® Hemostatic Matrix into blood vessels.
- 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.
- 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.

- Excess SURGIFLO® Hemostatic Matrix should be removed once hemostasis has been achieved, because of the possibility of dislodgment of the device or compression of other nearby anatomic structures.
- 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.
- The blue flexible applicator tip should not be trimmed to avoid exposing internal guidewire.
- The white straight applicator tip should be trimmed away from the surgical area. Cut a square angle to avoid creating a sharp tip. The tray can be used to contain the excess piece for discarding.

PRECAUTIONS

- 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.
- SURGIFLO® Hemostatic Matrix is supplied as a sterile product and cannot be resterilized. Unused open pouches of SURGIFLO® Hemostatic Matrix should be discarded.
- 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 incorporated into a fibrin clot, SURGIFLO® Hemostatic Matrix may swell up to 20% upon contact with additional fluid.
- 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.
- 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 40 µm transfusion filters of blood scavenging systems.
- 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.
- SURGIFLO® Hemostatic Matrix should not be used for the primary treatment of coagulation disorders.
- 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.
- The safety and effectiveness for use in urological procedures has not been established through a randomized clinical study.
- 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, 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, has 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 has 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%)

CLINICAL STUDIES

Study Design: An open-label, randomized, controlled, multi-center, unmasked study was conducted to evaluate the safety and effectiveness of 2 hemostatic agents. The study compared the SURGIFOAM® 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 SURGIFOAM® 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 2 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 were 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 SURGIFOAM® Sponge to another absorbable gelatin sponge (percent achieving hemostasis)

Minutes	Device	General Surgical	Cardiovascular	Orthopedic	Total
		% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)
3	SURGIFOAM® 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	SURGIFOAM® 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	SURGIFOAM® 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 SURGIFOAM® 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 SURGIFOAM® 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 SURGIFOAM® Sponge to induce anti-porcine 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 intraoperatively 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 (± 3 days) and at 30 days (± 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 sites, 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 complications such as synechiae or infections were reported in this study.

HOW SUPPLIED

SURGIFLO® Hemostatic Matrix Kit consists of:

1. A sterile tray with *all* sterile components to prepare the Flowable Gelatin Matrix
2. A sterile tray with *all* surface sterilized Thrombin kit components to prepare the Thrombin Solution

SURGIFLO® Hemostatic Matrix Kit is provided in the configuration shown in the table below.

SURGIFLO® Hemostatic Matrix Kit with Thrombin	
Flowable Gelatin Matrix Components	**Thrombin Components**
• A sterile pre-filled syringe with blue plunger containing the sterile Gelatin Matrix. The syringe is labeled **SURGIFLO™ Hemostatic Matrix** • A sterile empty syringe • A sterile liquid transfer cup • A sterile blue flexible applicator tip that is bendable in all directions • A sterile white applicator tip that can be trimmed to desired length	• A Thrombin vial, EVITHROM® Thrombin, Topical (Human), containing 2000 International Units (IU) of sterile lyophilized human thrombin powder for reconstitution • A needle-free syringe containing 2 mL of Sterile Water for Injection (Sterile WFI) • A sterile vial adapter

The package also contains the SURGIFLO® Hemostatic Matrix Kit Instructions for Use and tracking labels.

STORAGE AND HANDLING

- SURGIFLO® Hemostatic Matrix Kit should be stored dry at controlled room temperature 36°-77°F (2°-25°C).
- The Flowable Gelatin Matrix may be used up to eight (8) hours after mixing with the Thrombin Solution.
- For prescribing information on the Thrombin component, please refer to the EVITHROM® Thrombin, Topical (Human) Prescribing Information on page 9.
- SURGIFLO® Hemostatic Matrix Kit is for single use only.

DIRECTIONS FOR USE

Before use

Inspect the packages for signs of damage. If the package is damaged or wet, sterility cannot be assured and the contents should not be used.

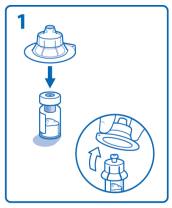
Open packages of SURGIFLO® Hemostatic Matrix Kit should be discarded, since they are not intended for reuse and/or resterilization.

Opening the tray with Flowable Gelatin Matrix and the tray with Thrombin kit components

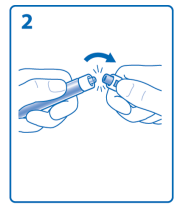
Open the outer packages and deliver the sterile inner trays to the sterile field using aseptic technique. Once placed in the sterile field, the sterile inner tray may be opened.

Preparing the Thrombin Solution inside the sterile field:

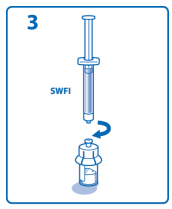
Flip off the cap from the *Thrombin vial,* leaving the aluminum ring and the rubber stopper in place. Peel off the lid from the *vial adapter* package.



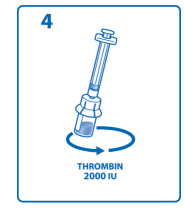
1. Place the *Thrombin vial* on a flat surface, seat the *vial adapter* on the center of the rubber stopper and push down until the spike penetrates the rubber stopper and the *vial adapter* snaps into place. Remove the blister package.



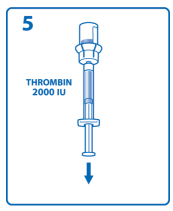
2. **Snap** off the tamper cap on the *needle-free syringe* containing the Sterile Water for Injection (Sterile WFI).



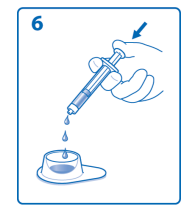
3. Connect and screw on the *needle-free syringe* to the *vial adapter*. Transfer the entire Sterile WFI into the *Thrombin vial*.



4. Gently swirl the *Thrombin vial* until the Thrombin Solution is clear.



5. Draw up the Thrombin Solution into the *needle-free syringe*. Label the *needle-free syringe*: "Thrombin 2000 IU".

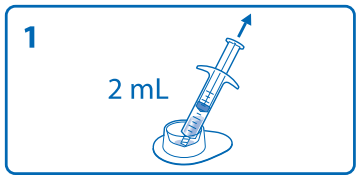


6. Disconnect the *needle-free syringe* from the *vial adapter* and transfer the Thrombin Solution into the sterile liquid transfer cup as shown in the next section (Figure 1).

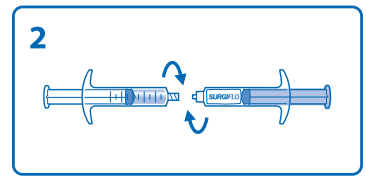
After reconstitution, discard the components used for the thrombin reconstitution.

Alternatively, the Thrombin may be reconstituted **outside** the sterile field. Be careful not to touch the rubber stopper of the vial. After reconstitution the Thrombin Solution should be transferred into the sterile liquid transfer cup using aseptic technique.
Place the sterile liquid transfer cup near the edge of the sterile field to receive the Thrombin Solution transfer without contaminating the sterile field.

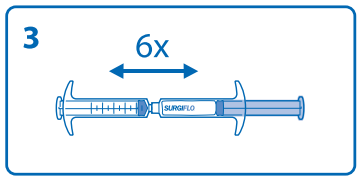
Preparing the Flowable Gelatin Matrix with sterile Thrombin Solution inside the sterile field:



1) Draw up 2 mL sterile Thrombin Solution from the sterile liquid transfer cup into the empty sterile syringe.

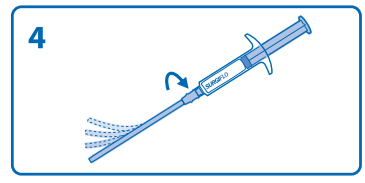


2) Connect syringes
Remove the blue cap from the end of the sterile pre-filled syringe with blue plunger containing the Gelatin Matrix. Attach this syringe to the sterile syringe containing the sterile Thrombin Solution.



3) Mix contents of the two syringes
Begin mixing by transferring the sterile Thrombin Solution into the sterile pre-filled syringe containing the Gelatin Matrix. Push the combined material back and forth 6 times until the consistency is even.

Once mixed, the hemostatic matrix should reside completely in the syringe with the blue plunger that is labeled **SURGIFLO™ Hemostatic Matrix**. Remove the empty syringe and discard.



4) Attach applicator tip
The product is now ready for clinical use.

Do not inject SURGIFLO® Hemostatic Matrix into blood vessels. See the Contraindications, Warnings, and Precautions.

For open procedures:

a. Identify the source of bleeding.
b. Deliver SURGIFLO® Hemostatic Matrix to the source of bleeding. SURGIFLO® Hemostatic Matrix can be used with or without the applicator tip attached to the syringe labeled **SURGIFLO™ Hemostatic Matrix**. Apply sufficient SURGIFLO® Hemostatic Matrix to cover the entire bleeding surface.
c. For tissue defects (cavities, divots, or craters) apply SURGIFLO® Hemostatic Matrix at the deepest part of the lesion, and continue applying material as the syringe (or applicator tip) is withdrawn from the lesion.
d. Apply a sterile saline moistened gauze over the SURGIFLO® Hemostatic Matrix to ensure the material remains in contact with the bleeding tissue.
e. After 1-2 minutes, lift the gauze and inspect the wound site. Once bleeding has ceased, irrigate excess SURGIFLO® Hemostatic Matrix away gently so as not to disturb the new clot.
f. In cases of persistent bleeding indicated by saturation and bleeding through the material, repeat application of SURGIFLO® Hemostatic Matrix.

For endoscopic and/or laparoscopic surgical procedures:

a. Prepare the selected endoscopic applicator according to the product's labeling.
b. Attach the selected endoscopic applicator tip to the **SURGIFLO™ Hemostatic Matrix** syringe. Make sure that the luer connection is secure.
c. Express SURGIFLO® Hemostatic Matrix to the end of the cannula. Introduce the cannula into the trocar port. Insert the cannula using caution not to express SURGIFLO® Hemostatic Matrix.
d. Carefully position the distal end of the endoscopic applicator to the site where SURGIFLO® Hemostatic Matrix is to be delivered. Be careful to avoid damaging tissue with the cannula.
e. While holding the endoscopic applicator in place, express SURGIFLO® Hemostatic Matrix to the bleeding site.
f. If applicable, detach **SURGIFLO™ Hemostatic Matrix** syringe and introduce the stylet to dispense remaining product in the length of the cannula.
g. Observe bleeding and repeat application of SURGIFLO® Hemostatic Matrix if necessary.
h. Carefully remove the endoscopic applicator from the trocar port when sufficient SURGIFLO® Hemostatic Matrix has been delivered to the bleeding site.

For endoscopic sinus surgery and epistaxis:

a. Deliver SURGIFLO® Hemostatic Matrix to the source of bleeding using the selected applicator tip attached to the syringe that is labeled **SURGIFLO™ Hemostatic Matrix**.
b. Apply sufficient SURGIFLO® Hemostatic Matrix to cover the entire bleeding surface. Using forceps or an appropriate instrument, carefully layer a sterile saline moistened gauze over the SURGIFLO® Hemostatic Matrix for 1-2 minutes to ensure the material remains in contact with the bleeding tissue.
c. 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 reapplication of SURGIFLO® Hemostatic Matrix, use a sterile saline moistened gauze to approximate the material to the tissue for another minute, and then inspect the site. Repeat reapplication if necessary.
d. Once hemostasis has been achieved, remove the gauze. 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 the post-operative 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).

SYMBOLS USED ON LABELING

	Store at controlled room temperature 36°–77°F (2°–25°C).		Device components are not made with natural rubber latex.
	See instructions for use.		Sterilized using irradiation.
	Do not reuse.		Sterilized using steam or dry heat.
	Do not resterilize.		Sterilized using ethylene oxide.
	Do not use if package is damaged or opened.		Manufacturer.
	Do not inject into blood vessels.		Re-order number.
	Caution, consult accompanying documents.		Use by: year, month and day.
	Distributed by.		Batch number.
	Designates the packaging material to which it is applied is recyclable. Recycling programs may not exist in your area.		

Leaflet prepared: 09/2016

EVITHROM® Thrombin, Topical (Human)
Prescribing Information

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)]
Lyophilized Powder for Solution
For topical use
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

- **For topical use only. DO NOT INJECT** *(2.2)*.
- Apply EVITHROM® on the surface of bleeding tissue only.
- 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)*.

DOSAGE FORMS AND STRENGTHS

EVITHROM® is a lyophilized powder for solution containing 2000 (1600–2400) units of human thrombin. After reconstituted, the final solution contains 1000 (800–1200) units/ml of EVITHROM® *(3)*.

CONTRAINDICATIONS

- **Do not use in individuals known to have an anaphylactic or severe systemic reaction to EVITHROM® or 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)*.
- **Hypersensitivity reactions, including anaphylaxis, may occur** *(5.1)*.

ADVERSE REACTIONS

- The most common adverse reactions (incidence 2%) were prolonged activated partial thromboplastin time, increased INR, decreased lymphocyte count, prolonged prothrombin time and increased neutrophil count *(6)*.
- None of the patients treated with EVITHROM® developed antibodies to human thrombin or to human Factor V/Va. The clinical significance of these findings is unknown *(6)*.

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

Animal Reproduction studies have not been conducted with EVITHROM®. EVITHROM® should only be used in pregnancy if clearly indicated *(8.1)*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: August/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

** 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

2.1 Dose

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. 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.

2.2 Preparation

- Use aseptic technique when handling vials and syringes.
- Remove the flip-off plastic cap from the vial to expose the rubber stopper.
- Reconstitute the lyophilized human thrombin powder with 2 ml of sterile Water for Injection, USP using the provided reconstitution device.
- 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.

2.3 Application Techniques

Apply only on the surface of bleeding tissue.

EVITHROM® Use alone

- Sponge target surface (do not wipe) or suction free of blood before application.
- Flood the surface with EVITHROM® using a sterile syringe and small gauge needle.
- Avoid sponging after treatment, to ensure that the clot remains securely in place.

EVITHROM® in conjunction with Absorbable Gelatin Sponge, USP

- Prepare the desired shape of the Absorbable Gelatin Sponge, USP (see Absorbable Gelatin Sponge, USP circular for additional instructions for use).
- Transfer EVITHROM® into a sterile container using aseptic techniques.
- Immerse gelatin sponge into 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.

3 DOSAGE FORMS AND STRENGTHS

EVITHROM® is a sterile lyophilized powder for solution 2000 (1600–2400) units of lyophilized human thrombin powder for reconstitution. After reconstituted, the final solution contains 1000 (800–1200) units/ml of human thrombin.

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 an anaphylactic or severe systemic reaction to EVITHROM® or to human blood products.**
- **Do not use for the treatment of severe or brisk arterial bleeding.**

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis

There is a risk of thrombosis if absorbed systemically. Apply topically only.

5.2 Anaphylactic/Hypersensitivity Reactions

Anaphylactic reactions may occur in rare cases. No adverse events of this type were reported during the conduct of the clinical trials. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

5.3 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.

6 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.

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.

In a multicenter, prospective, controlled, randomized, double-blinded clinical trial 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 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 trial 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%)**
Pruritus	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). 7.9% of the subjects treated with bovine thrombin (control group) developed antibodies to bovine thrombin and 9.5% 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with EVITHROM®. It is also not known whether EVITHROM® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EVITHROM® should be given to a pregnant woman only if clearly needed.

Evaluation of the reproduction and development toxicity has been limited to the evaluation of embryo-fetal development of TnBP and Triton X-100 formulated in saline in rat and rabbit (see *Section 13 NONCLINICAL TOXICOLOGY* for more information).

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 clinical trial. No differences in safety or effectiveness were observed between the elderly and younger patients. Greater susceptibility of older patients to adverse reactions cannot be ruled out.

11 DESCRIPTION

EVITHROM® is a sterile lyophilized powder of purified human thrombin (1600–2400 units) of white to slightly yellowish color. When reconstituted, EVITHROM® solution, pH 6.8–7.2, is clear to slightly opalescent and colorless to slightly yellowish. Other inactive ingredients are Calcium chloride, Human albumin, Mannitol, Sodium acetate.

EVITHROM® is made from pooled Human Source 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. Additionally, the plasma units are tested by licensed Nucleic Acid Testing (NAT) for HIV-1, HCV, HBV, HAV and parvovirus B19. 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, HCV NAT and for parvovirus B19 by 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	MVM
	Reduction factor (log_{10})						
SD Treatment	>5.8	>5.0	>4.6	>4.2	Not Done	Not Done	Not Done
Nanofiltration	>4.6	Not Done	>5.6	>5.7	>7.4	>7.5	>6.3
Global Reduction Factor	**>10.4**	**>5.0**	**>10.2**	**>9.9**	**>7.4**	**>7.5**	**>6.3**

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
MVM: Minute Virus of Mouse

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.

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 5 µg/ml.

14 CLINICAL STUDIES

EVITHROM® was compared with bovine thrombin in a multicenter, prospective, randomized, controlled, double-blinded clinical trial 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 comparable to treatment with bovine thrombin in achieving hemostasis within:

- 10 minutes of product application and
- 6 and 3 minutes of product application.

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

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

[1] 95% CI is for the ratio of proportions of success

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

Table 4: Efficacy at 6 minutes (ITT population)

Surgical Specialty	Treatment Group: # Successes/N (%)		Ratio Human/Bovine	95% CI for Ratio Human/Bovine[1,2]
	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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

EVITHROM® is supplied in a single-use 2 ml vial containing 2000 (1600–2400) units of lyophilized human thrombin powder for reconstitution in 2 ml Water for Injection, USP.

NDC 63713-461-02

- Store EVITHROM® powder vials at 2–25°C (36–77°F) for up to 2 years.
- Discard if the packaging of EVITHROM® is damaged.
- Keep the vials protected from light.
- Store reconstituted EVITHROM® solution at room temperature for up to 8 hours.
- Do not freeze or refrigerate EVITHROM® once it has been reconstituted.
- Discard unused contents.

17 PATIENT COUNSELING INFORMATION

Inform patients of the following:

- 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 if leg tenderness or swelling, chest pain, or shortness of breath appears.

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VISTASEAL™

Fibrin Sealant (Human)
Frozen solutions of fibrinogen and thrombin

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VISTASEAL™ (Fibrin Sealant (Human))
Frozen solutions of fibrinogen and thrombin
For Topical Use Only
Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Dosage and Administration (2)	4/2019
Warnings and Precautions (5)	4/2019

INDICATIONS AND USAGE

VISTASEAL™ is indicated as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VISTASEAL is effective in heparinized patients. (1)

DOSAGE AND ADMINISTRATION

For Topical Use Only.

- After thawing, use VISTASEAL within 48 hours if stored at 2 °C - 8 °C (36 °F - 46 °F), or within 24 hours if stored at room temperature (20 °C - 25 °C (68 °F - 77 °F)), if it remains sealed in the original packaging. (2.2, 16)
- Prior to applying VISTASEAL, use standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) to dry the surface area of the target bleeding site. (2.3)
- Apply VISTASEAL by dripping or spraying. When applying VISTASEAL using a spray device, ensure that the distance from the tissue is within the recommended ranges for the applicator tip used. (2.3, 2.4)
- Apply a sufficient volume of VISTASEAL to entirely cover the intended application area with a thin layer. (2.1, 2.4)

DOSAGE FORMS AND STRENGTHS

VISTASEAL is supplied as a kit consisting of two separate packages:

- A package containing one syringe each of human fibrinogen 80 mg/mL (component 1) and human thrombin 500 IU/mL (component 2) sterile frozen solutions which are assembled in a syringe holder.
- A package containing a VISTASEAL Dual Applicator with two additional Airless Spray Tips.

VISTASEAL is available in the following package sizes:

Package size (Total volume)	Human fibrinogen	Human thrombin
2 mL	1 mL	1 mL
4 mL	2 mL	2 mL
6 mL	3 mL	3 mL
10 mL	5 mL	5 mL

CONTRAINDICATIONS

- Do not inject directly into the circulatory system. (4)
- Do not use for the treatment of severe or brisk arterial bleeding.
- Do not use in patients with history of anaphylaxis or severe systemic reactions to human blood products. (4)
- Do not use VISTASEAL for spraying unless the minimum recommended distance from the applicator tip to the bleeding site can be achieved. (2.3, 4)

WARNINGS AND PRECAUTIONS

- Thromboembolic events may occur if VISTASEAL is administered intravascularly. (5.1)
- Hypersensitivity reactions can occur. (5.2)
- May carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (reported in >1% of clinical trial subjects) were nausea and procedural pain. (6)

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

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VISTASEAL is indicated as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. VISTASEAL is effective in heparinized patients.

2 DOSAGE AND ADMINISTRATION

For topical use only.

2.1 Dosage

Individualize application of the fibrin sealant. Individual doses typically ranged from 0.3 to 18.0 mL in the clinical studies. Larger volumes may be required for surgical procedures other than those included in the clinical studies. The approximate surface area coverage for each VISTASEAL package size is provided in Table 1.

Table 1. Surface Area Coverage

VISTASEAL package size	Surface area coverage (cm^2) Application by dripping or spray (1 mm thick layer)
2 mL	16 - 22
4 mL	32 - 44
6 mL	48 - 66
10 mL	80 - 110

Dose depends on variables including, but not limited to, the type of surgical intervention, the size of the area, the intended application method, and the number of applications.
Apply a sufficient volume of VISTASEAL to entirely cover the intended application area with a thin layer. Repeat the application if necessary.

2.2 Preparation and Handling

Prepare and administer the product only according to the instructions and with the recommended devices.
Remove carton from freezer, open it and take out the two blisters.
Place the blister containing the VISTASEAL Dual Applicator at room temperature until the VISTASEAL Fibrin Sealant (Human) is ready to use.

Room Temperature Thawing (preferred method)
Thaw blister with VISTASEAL pre-filled syringes at room temperature using the following steps:

1. Place the blister containing the syringe holder with pre-filled syringes on a surface at room temperature (20 °C - 25 °C, (68 - 77 °F))
   - for approximately 70 minutes for the 2 mL and the 4 mL package sizes
   - for approximately 90 minutes for the 6 mL and the 10 mL package sizes

After thawing, it is not necessary to warm the product for its use.
After thawing, the solutions must be clear to slightly opalescent and colorless to pale yellow. Do not use solutions that are cloudy or have deposits.

Post-Thawing Storage:
After thawing, the kit containing the VISTASEAL syringe holder with pre-filled syringes and Dual Applicator can be stored before use for not more than 48 hours in the refrigerator at 2 - 8 °C (36 - 46 °F) or 24 hours at room temperature (20 - 25 °C (68 - 77 °F)) if it remains sealed in the original packaging. Once the blisters are opened, use VISTASEAL immediately during the surgery and discard any unused contents.
Once thawed, do not refreeze.

Transferring instructions:

1. After thawing, remove the blister from the surface at room temperature or from the refrigerator at 2 - 8 °C (36 - 46 °F).
2. Open the blister and make the VISTASEAL syringe holder with pre-filled syringes available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field. See Figure 1.

Figure 1

Sterile Water Bath (Quick Thawing)
Thaw VISTASEAL pre-filled syringes inside the sterile field in a sterile thermostatic water bath at a temperature not higher than 37 °C (99 °F) using the following steps:
NOTE: Once the VISTASEAL blisters are opened, use the product immediately during surgery. Use sterile technique to avoid the possibility of contamination due to improper handling; and follow the steps below accurately. Do not remove the syringe luer cap until thawing is complete and the Dual Applicator is ready to be attached.

1. Open the blister and make the VISTASEAL syringe holder with pre-filled syringes available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field. See Figure 1.
2. Place the syringe holder with pre-filled syringes directly into the sterile water bath ensuring that it is completely immersed in the water. See Figure 2.
3. At 37 °C, the time needed is approximately 5 minutes for the 2 mL, 4 mL, 6 mL, and 10 mL package sizes, but must not be left at this temperature for longer than 10 minutes.
   The temperature of the water bath must not exceed 37 °C.
4. Dry the syringe holder with pre-filled syringes after thawing, using a sterile surgical gauze.

Figure 2

After thawing, the solutions must be clear to slightly opalescent and colorless to pale yellow. Do not use solutions that are cloudy or have deposits.
Use VISTASEAL immediately during the surgery and discard any unused contents.
Connection instructions

1. Open the blister and make the VISTASEAL Dual Applicator and two additional Airless Spray Tips available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field.
2. Hold the VISTASEAL Fibrin Sealant (Human) syringe holder with syringe luer caps pointed upward. See Figure 3.
3. Unscrew and discard the syringe luer cap of both fibrinogen and thrombin syringes. See Figure 3.

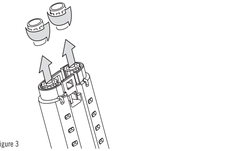

Figure 3

4. Hold the syringe holder with the luers pointed upward. To remove air bubbles from syringes, strike gently the side of the syringe holder one or two times while keeping the syringe holder in an upright position and lightly depress the plunger to eject air. See Figure 4.

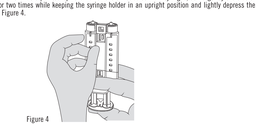

Figure 4

5. Attach the Dual Applicator. See Figure 5.
   NOTE: Do not depress plunger during attachment or prior to intended use because the two biologic components will pre-mix in the Airless Spray Tip, forming a fibrin clot that prevents dispensing. See Figure 6.

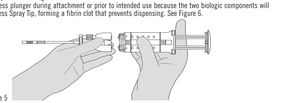

Figure 5

Figure 6

6. Tighten luer locks and ensure the Dual Applicator is firmly attached. The device is now ready to use.

2.3 Administration

Apply VISTASEAL Fibrin Sealant (Human) using the syringe holder and plunger supplied.
Apply VISTASEAL Fibrin Sealant (Human) using the Dual Applicator provided with the product. Applicator tips cleaned by the FDA for specific use with the VISTASEAL Fibrin Sealant (Human) may also be used. When using the provided Dual Applicator, follow the connection instructions in the above section for Preparation. When using other applicator tips, follow the instructions for use that are provided with the applicator tips.
Before administration of VISTASEAL Fibrin Sealant (Human):

- To prevent tissue adhesion at undesired sites, protect (cover) parts of the body outside the intended application area. *[see Dosage and Administration (2.4)]*
- Use standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) to dry the surface area of the target bleeding site.

Application by spraying

1. Grasp and bend the Dual Applicator to the desired position. Tip will retain its shape.
2. Position the Airless Spray Tip at least 2 cm away from the target tissue. Apply firm even pressure to the plunger to spray the fibrin sealant. Increase distance accordingly to achieve desired coverage of the target area.
3. If expression is stopped for any reason, change the Airless Spray Tip. To change the Airless Spray Tip, remove the device from the patient and unscrew the used Airless Spray Tip. See Figure 7. Place the used Airless Spray Tip away from the spare Airless Spray Tips. Wipe the end of the applicator using dry or moist sterile surgical gauze. Then, connect a new Airless Spray Tip provided in the package and ensure it is firmly connected before use.
   NOTE: Red indicator will not be visible if Airless Spray Tip is properly connected. See Figure 8.
   NOTE: Do not continue pushing the plunger in an attempt to clear the fibrin clot within the Airless Spray Tip; otherwise the applicator may become unusable.
   NOTE: Do not trim the Dual Applicator to avoid exposing internal wire.

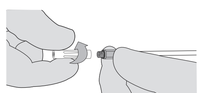

Figure 7

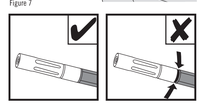

Figure 8

Application by dripping

1. Remove the Airless Spray Tip portion of the spray and drip tip by unscrewing the Airless Spray Tip. See Figure 7.
2. Grasp and bend the drip tip to the desired position. Tip will retain its shape.
3. During dripping, keep the end of the drip tip as close to the tissue surface as possible without touching the tissue during application.
4. Apply individual drops to the surface area to be treated. To prevent uncontrolled clotting, allow the drops to separate from each other and from the end of the drip tip.
   NOTE: Do not reconnect a used drip tip after it has been removed from the adapter; otherwise a clot may form inside the drip tip and the applicator may become unusable.

2.4 Application precautions

- Before administration of VISTASEAL, protect (cover) parts of the body outside the desired application area to prevent tissue adhesion at undesired sites. *[see Dosage and Administration (2.3)]*
- Apply VISTASEAL as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process. *[see Dosage and Administration (2.1)]*
- Only spray VISTASEAL if it is possible to accurately judge the distance from the spray tip to the tissue surface. *[see Dosage and Administration (2.3)]*
- No clinical data are available to support the use of this product in neurosurgery or application through a flexible endoscope for treatment of bleeding.

3 DOSAGE FORMS AND STRENGTHS

VISTASEAL is supplied as a kit consisting of two separate packages.

- A package containing one syringe each of human fibrinogen 80 mg/mL (component 1) and human thrombin 500 IU/mL (component 2) sterile frozen solutions which are assembled on a syringe holder.
- A package containing a Dual Applicator with two additional Airless Spray Tips.

The available package sizes of VISTASEAL are shown in Table 2.

Table 2. VISTASEAL Package Sizes

Package size (Total volume)	Human fibrinogen	Human thrombin
2 mL	1 mL	1 mL
4 mL	2 mL	2 mL
6 mL	3 mL	3 mL
10 mL	5 mL	5 mL

4 CONTRAINDICATIONS

- Do not inject directly into the circulatory system. *[see Warnings and Precautions (5.1)]*
- Do not use for the treatment of severe or brisk arterial bleeding. In these situations, blood flow will wash away VISTASEAL and prevent hemostasis.
- Do not use VISTASEAL in patients known to have anaphylactic or severe systemic hypersensitivity reactions to the administration of human blood products. *[see Warnings and Precautions (5.2)]*
- Do not use VISTASEAL for spraying unless the minimum recommended distance from the applicator tip to the bleeding site can be achieved. *[see Dosage and Administration (2.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis

Life-threatening thromboembolic complications may occur if VISTASEAL is administered intravascularly.

5.2 Hypersensitivity

Allergic-type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, discontinue the administration of VISTASEAL immediately. Treat the reaction accordingly.

5.3 Transmissible Infectious Agents

Because VISTASEAL is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and theoretically, the Creutzfeldt-Jakob (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. All suspected infections related to this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC at 1-800-520-2807. The physician should discuss the risks and benefits of the use of VISTASEAL with the patient. *[see Patient Counseling Information (17)]*

6 ADVERSE REACTIONS

The most common adverse reactions (reported in > 1% of clinical trial subjects) were nausea and procedural pain.

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 cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
Three clinical trials were conducted using the same general design, with each being randomized and active controlled. The types of surgeries included in each trial were different. Across all trials, 26% were vascular surgeries, 37% were parenchymous tissue surgeries, and 37% were soft tissue surgeries. The clinical trials were conducted with Fibrin Sealant (Human) using Fibrijet® drip or spray applicators.
Fibrin Sealant (Human) was used to treat vascular bleeding during vascular surgery, or parenchymal bleeding during hepatic surgery, or soft tissue bleeding during retroperitoneal or pelvic surgery, abdominoplasties, or mastopexies, across all clinical trials, involving 500 trial subjects treated with Fibrin Sealant (Human), and 377 control subjects. The number of trial subjects treated with Fibrin Sealant (Human) for each type of surgery was 168 for vascular surgery, 163 for parenchymal surgery, and 169 for soft tissue surgery.
The Fibrin Sealant (Human) treatment group had a mean age of 57 years (standard deviation: 15.6 years; range: 0.3 to 86 years). The median age was 60 years. There were 11 subjects younger than 18 years old. There were 51% male subjects. 87% of the subjects exposed to Fibrin Sealant (Human) were White.
The mean volume of Fibrin Sealant (Human) used per subject and target bleeding site was 7 mL (standard deviation 3.5) and ranged from 0.3 to 18 mL. The median volume was 6 mL. Exposure to Fibrin Sealant (Human) consisted of a single intraoperative administration.
The clinical safety database included all subjects who received any amount of Fibrin Sealant (Human) in all clinical studies, with no exclusions.
In the Fibrin Sealant (Human) treatment group, 13% of trial subjects experienced one or more adverse reactions, and 8% of control subjects experienced one or more adverse reactions.
The adverse reactions shown in Tables 3-6 were evaluated as having a possible causal relationship to treatment with Fibrin Sealant (Human) and occurred in >1% of subjects.

Table 3. Adverse Reactions Occurring in >1% of Subjects in Vascular, Parenchyma, and Soft Tissue Surgery

Preferred Term	N = 500 n (%);
Nausea	6 (1)
Procedural pain	10 (2)

Table 4. Adverse Reactions Occurring in >1% of Subjects in Vascular Surgery

Preferred Term	N = 168 n (%)
Nausea	2 (1)
Pyrexia (fever)	2 (1)
Procedural pain	4 (2)
Vascular graft complication	2 (1)
Parvovirus B19 test positive	2 (1)
Urinary retention (Unable to empty the bladder completely)	2 (1)

Table 5. Adverse Reactions Occurring in >1% of Subjects in Parenchyma Surgery

Preferred Term	N = 163 n (%)
Postprocedural bile leak	2 (1)
Procedural pain	2 (1)
Pulmonary embolism (Blood clot in the lungs)	2 (1)
Deep vein thrombosis (Blood clot that forms in a vein deep)	2 (1)

Table 6. Adverse Reactions Occurring in >1% of Subjects in Soft Tissue Surgery

Preferred Term	N = 169 n (%)
Anemia (Low red blood cells)	2 (1)
Leukocytosis (Increased white blood cells)	2 (1)
Ileus (Decreased or absent movement of the stomach or intestine)	2 (1)
Nausea	4 (2)
Procedural pain	4 (2)
Alanine aminotransferase increased	2 (1)
Aspartate aminotransferase increased	2 (1)
Hypocalcaemia (Low serum calcium)	2 (1)
Hypokalaemia (Low serum potassium)	2 (1)
Hyponatraemia (Low serum sodium)	2 (1)
Prothrombin time prolonged (Increased bleeding time)	2 (1)
Headache	2 (1)
Insomnia	2 (1)
Pruritus (Itching)	4 (2)
Hypertension	2 (1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data with VISTASEAL use in pregnant women. Animal reproduction studies have not been performed with VISTASEAL. It is unknown whether VISTASEAL can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

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

8.4 Pediatric Use

A total of 11 out of 500 subjects administered Fibrin Sealant (Human) in the clinical trials were pediatric subjects. Of these 11 subjects, 5 were infants aged less than 2 years, 5 were children between the ages of 2 and 11 years, and 1 was an adolescent aged between 12 and 16 years. Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials included 172 subjects aged 65 years or older treated with Fibrin Sealant (Human). No differences in safety or effectiveness were observed between these subjects and younger subjects.

11 DESCRIPTION

VISTASEAL is a two-component fibrin sealant consisting of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) sterile solutions filled in syringes which are assembled in a syringe holder.
VISTASEAL is supplied as frozen solutions. After thawing, the human fibrinogen and human thrombin solutions are clear or slightly opalescent and colorless or pale yellow. VISTASEAL does not contain any preservatives.
Fibrinogen
Component 1 is a sterile solution, pH 6.5 - 8.0, which contains concentrated human fibrinogen and excipients. Fibrinogen is a protein from human blood that forms a clot when combined with thrombin. The composition of the human fibrinogen solution is as follows:
Active ingredient: human fibrinogen (80 mg/mL)
Other ingredients: sodium citrate, sodium chloride, arginine, L-isoleucine, L-glutamic acid monosodium and water for injection.
Thrombin
Component 2 is a sterile solution, pH 6.0 – 8.0, which contains purified human thrombin and excipients. Thrombin is a specific protease that activates clotting of the fibrinogen to form the clot. The composition of the human thrombin solution is as follows:
Active ingredient: human thrombin (500 IU/mL)
Other ingredients: calcium chloride, human albumin, sodium chloride, glycine and water for injection.
The starting material for the production of both fibrinogen and thrombin components of VISTASEAL is pooled human Source Plasma obtained from FDA-licensed plasma collection centers in the United States. Cohn's plasma fractionation method is used to obtain Fraction I, which is the starting material for the production of fibrinogen, and the prothrombin complex isolated from supernatant of Fraction I, which is the starting material for the production of thrombin. The purification process of fibrinogen includes solvent/detergent treatment, three glycine precipitation steps, and double nanofiltration using 35-nm and 20-nm filters. The purification process of thrombin includes solvent/detergent treatment, ion exchange chromatography, and double nanofiltration through 15-nm filters. After nanofiltration, the fibrinogen and thrombin solutions are formulated, sterile filtered, aseptically filled in syringes, packaged, sterilized, and frozen.
Viral safety
Individual plasma donations used in the manufacture of VISTASEAL are collected in FDA-licensed plasma donation centers in the U.S. and are tested for viral markers in compliance with the U.S. regulatory requirements. In addition, mini-pools of plasma units are tested as an in-process control for hepatitis A virus (HAV) and parvovirus B19 (B19V) using validated nucleic acid testing (NAT) methods. All the tests must be non-reactive (negative) except for B19V, for which the limit in plasma manufacturing pools does not exceed a titer of 10^3 IU/mL. The manufacturing plasma pool is also tested with NAT for HBV, HCV, and HIV, and all the tests must be non-reactive (negative).
The manufacturing processes for fibrinogen and thrombin include processing steps which are designed to reduce the risk of viral transmission. Both components have two discrete steps with viral clearance capacity, namely solvent/detergent treatment (with 1.0% (v/v) Tween 80/0.30% (v/v) tri-n-butyl phosphate (TNBP) for 6.0 – 6.5 hours at 27.0 ± 1.5 °C for fibrinogen or 25 ± 1 °C for thrombin), validated to inactivate enveloped viruses, and a nanofiltration step validated to remove non-enveloped and enveloped viruses (35-nm and 20-nm filters for fibrinogen and two 15-nm filters for thrombin). Additionally, the glycine precipitation steps contribute to the overall safety of the product in the purification process of human fibrinogen. The Fraction I precipitation and ion-exchange chromatography steps contribute to the overall safety of the product in the purification process of human thrombin.
The viral clearance capacity of these viral inactivation/removal procedures has been validated in small-scale *in vitro* studies using relevant and model viruses with a range of physico-chemical characteristics. The results of viral clearance validation studies are summarized in Tables 7 and 8.

Table 7. Global Virus Reduction Factors (Log_{10}) for Human Fibrinogen

Manufacturing step	Virus reduction factor (log_{10})*					
	Enveloped viruses				Non-enveloped viruses	
	HIV-1	PRV	WNV	BVDV	HAV	PPV
S/D treatment	≥ 5.33	≥ 6.80	≥ 5.20	≥ 5.60	n.a.	n.a.
Glycine precipitations	n.d.	n.d.	n.d.	n.d.	5.21	2.09
Nanofiltration 35 nm and 20 nm	≥ 5.57	≥ 6.09	≥ 4.51	≥ 4.53	5.22	4.37
Global virus reduction factor (log_{10})	≥ 10.90	≥ 12.89	≥ 9.71	≥ 10.13	10.43	6.46

Table 8. Global Virus Reduction Factors (Log_{10}) for Human Thrombin

Manufacturing step	Virus reduction factor (log_{10})*					
	Enveloped viruses				Non-enveloped viruses	
	HIV-1	PRV	WNV	BVDV	HAV	PPV
Fraction I precipitation	< 1.0	2.13	2.78	1.34	1.18	< 1.0
S/D treatment	≥ 5.52	≥ 5.85	≥ 5.94	≥ 5.09	n.a.	n.a.
SP-Sepharose XL chromatography	n.d.	n.d.	n.d.	n.d.	4.61	3.97
Double nanofiltration 15 nm	≥ 4.03	≥ 5.95	≥ 5.42	≥ 4.93	6.56	6.14
Global virus reduction factor (log_{10})	≥ 9.55	≥ 13.93	≥ 14.14	≥ 11.36	12.35	10.11

*: Reduction factor below 1 log_{10} is not considered in calculating the global virus reduction. n.d.: Not done; n.a.: Not applicable; BVDV: bovine viral diarrhea virus, model for HCV; WNV: West Nile virus; PRV: pseudorabies virus, model for large enveloped DNA viruses; PPV: porcine parvovirus, model for B19V.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VISTASEAL contains human fibrinogen and human thrombin. When applied onto the wound site and mixed, these biological components generate a cross-linked fibrin clot in a process that recreates the last stage of the human blood coagulation system. Fibrinogen is converted into fibrin monomers and fibrinopeptides by thrombin. The fibrin monomers aggregate and form a fibrin clot which stops the bleeding. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both the conversion of fibrinogen and the crosslinking of fibrin.

12.2 Pharmacodynamics

There are no relevant pharmacodynamic data on VISTASEAL.

12.3 Pharmacokinetics

VISTASEAL is metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis. No pharmacokinetic studies were conducted for VISTASEAL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of VISTASEAL or its effects on fertility.

14 CLINICAL STUDIES

Vascular surgery
A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of Fibrin Sealant (Human) as adjunct to hemostasis in vascular surgery. Subjects underwent vascular surgical procedures utilizing polytetrafluoroethylene graft material on proximal end-to-side arterial anastomosis or upper extremity vascular access arterial anastomosis. The clinical trial was conducted with Fibrin Sealant (Human) using a Fibrijet® applicator. Fibrin Sealant (Human) was shown to be superior to the control group (manual compression) when comparing the proportion of subjects in each group who achieved hemostasis by 4 minutes (Table 9). Superiority was also established at 10 minutes. The median time to hemostasis was significantly shorter (p-value <0.001) in the Fibrin Sealant (Human) treatment group (4.0 minutes) compared to the control group (≥10.0 minutes).

Table 9. Efficacy Results in Vascular Surgery (ITT Population)*

Efficacy endpoints	Fibrin Sealant (Human) N=109 n (%)	Control N=57 n (%)	Ratio of proportions† (95% CI)	P-value
Hemostasis by 4 minutes	83 (76.1)	13 (22.8)	3.3 (2.0, 5.4)	<0.001
Hemostasis by 10 minutes	96 (88.1)	26 (45.6)	1.9 (1.4, 2.6)	<0.001

*Intent-to-treat (ITT) population: includes all subjects randomized to Fibrin Sealant (Human) or control.
†The ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups (Fibrin Sealant (Human) relative to control).
CI = confidence interval.
Tabulated efficacy results are cumulative results.

Parenchyma surgery
A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of Fibrin Sealant (Human) as adjunct to hemostasis in parenchyma surgery. Subjects underwent liver resections. The clinical trial was conducted with Fibrin Sealant (Human) using a Fibrijet® applicator. Fibrin Sealant (Human) was shown to be superior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes (Table 10).
The median time to hemostasis was significantly shorter (p-value <0.001) in the Fibrin Sealant (Human) treatment group (2.0 minutes) compared to the control group (3.0 minutes).

Table 10. Efficacy Results in Liver Surgery (ITT Population)*

Efficacy endpoints	Fibrin Sealant (Human) N = 111 n (%)	Control N=113 n (%)	Ratio of proportions† (95% CI)	P-value
Hemostasis by 4 minutes	103 (92.8)	91 (80.5)	1.2 (1.0, 1.3)	0.010
Hemostasis by 2 minutes	62 (55.9)	47 (41.6)	1.3 (1.0, 1.8)	0.045

*Intent-to-treat (ITT) population: includes all subjects randomized to Fibrin Sealant (Human) or control.
†The ratio of proportions of subjects meeting the efficacy endpoint in the two treatment groups (Fibrin Sealant (Human) relative to control).
CI = confidence interval.
Tabulated efficacy results are cumulative results.

Soft tissue surgery
A prospective, randomized, controlled clinical study was performed to evaluate the safety and efficacy of Fibrin Sealant (Human) as adjunct to hemostasis in soft tissue bleeding during retroperitoneal and pelvic surgical procedures, and during mastopexies and abdominoplasties.
The clinical trial was conducted with Fibrin Sealant (Human) using a Fibrijet® applicator. Fibrin Sealant (Human) was shown to be superior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes (Table 11).

Table 11. Efficacy results in retroperitoneal and pelvic surgery, mastopexies and abdominoplasties (ITT population)*

Efficacy endpoints	Fibrin Sealant (Human) N = 116 n (%)	Control N=108 n (%)	Ratio of proportions† (95% CI)	P-value
Hemostasis by 4 minutes	96 (82.8)	84 (77.8)	1.1 (0.9, 1.2)	0.401

*Intent-to-treat (ITT) population: includes all subjects randomized to Fibrin Sealant (Human).
†The ratio of proportions of subjects meeting the efficacy endpoint in the two treatment groups (Fibrin Sealant (Human) relative to control).
CI = confidence interval.
Tabulated efficacy results are cumulative results.

16 HOW SUPPLIED/STORAGE AND HANDLING

VISTASEAL is supplied as a single-dose kit comprised of two pre-filled syringes containing sterile frozen solutions of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2), which are assembled in a single syringe holder. The syringe plungers are connected by a plunger link to ensure simultaneous application of the biological components. One Dual Applicator with two additional Airless Spray Tips is co-packaged with the product for application by spraying or dripping. The Airless Spray Tips are radiopaque. See Figure 9.

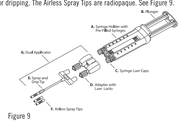

Figure 9

The available package sizes for VISTASEAL are shown in Table 12.

Table 12. VISTASEAL Package Sizes and NDC numbers

VISTASEAL Package Size			NDC Numbers	
Total Volume	Human fibrinogen	Human thrombin	Carton	Blister label
2 mL	1 mL	1 mL	61953-0011-1	61953-0011-2
4 mL	2 mL	2 mL	61953-0012-1	61953-0012-2
6 mL	3 mL	3 mL	61953-0013-1	61953-0013-2
10 mL	5 mL	5 mL	61953-0014-1	61953-0014-2

Storage
Store the frozen kit (VISTASEAL Fibrin Sealant (Human) with VISTASEAL Dual Applicator) in a freezer (at -18 °C (0 °F) or colder) for up to 2 years. The cold storage condition must not be interrupted until use. Thaw before use. Once thawed, do not refreeze.
After thawing, VISTASEAL can be stored before use for not more than 48 hours at 2 - 8 °C (36 - 46 °F) or 24 hours at room temperature (20 - 25 °C (68 - 77 °F)) if it remains sealed in the original packaging. Once the package is opened, use VISTASEAL immediately during the surgery and discard any unused contents.
Keep the sterilized blister in the outer carton to protect from light.
Do not use after the expiration date printed on the outer carton and container labels. Discard if the package is damaged.

17 PATIENT COUNSELING INFORMATION

Instruct patients to immediately report to their physician symptoms of thrombosis or embolism which may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body *[see Thrombosis (5.1)]*.
Inform patients that VISTASEAL is made from human plasma and may carry a risk of transmitting infectious agents (e.g., viruses, the vCJD agent and, theoretically, the CJD agent). Instruct patients to report any symptoms that concern them and might be caused by infections.

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