Product Monograph

EVICEL®
Fibrin Sealant (Human)
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Overview
EVICEL® Overview

EVICEL® is a plasma cryoprecipitate-based sealant that consists of two components: 1) Biological Active Component 2 (BAC2 [Human Fibrinogen Solution]) which consists predominantly of fibrinogen; and 2) Thrombin. Thrombin is a highly specific protease that transforms the fibrinogen contained in BAC2 (Human Fibrinogen Solution) into fibrin. The thrombin solution contains highly purified human thrombin and calcium chloride for activation of clotting of the final combined product.

EVICEL® is provided as a single-use human surgical sealant kit consisting of two packages: The first containing one vial each of frozen sterile solutions of BAC2 (Human Fibrinogen Solution) and thrombin, and the second containing the sterile application device. It is the only totally human protein-derived, bovine- and aprotinin-free fibrin sealant commercially available in the United States.

After the BAC2 (Human Fibrinogen Solution) and thrombin solutions are thawed, they are drawn into a unique tri-lumen (two syringe lumens and one air lumen for spraying) catheter application device. The solutions mix as they exit the catheter at the time of administration. The mixture is applied topically by dripping or spraying. Once applied, the two components interact to form a stable, transparent clot.

EVICEL® is a new version of a previously available fibrin sealant called CROSSEAL* Fibrin Sealant (Human). CROSSEAL Fibrin Sealant received FDA approval in the United States in March 2003. The introduction of EVICEL® is to offer a fibrin sealant with the same features and benefits as CROSSEAL Fibrin Sealant, but without the need for an antifibrinolytic agent to ensure its stability.

Antifibrinolytic agents commonly used in the formulation of fibrin sealants include tranexamic acid (TA; used in CROSSEAL Fibrin Sealant), and aprotinin (used in TISSEEL™ from Baxter). CROSSEAL Fibrin Sealant with tranexamic acid was contraindicated for use in contact with cerebrospinal fluid (CSF) or dura mater. Aprotinin can result in severe allergic or anaphylactic reactions with symptoms including flush, urticaria, pruritis, nausea, drop in blood pressure, tachycardia, bradycardia, dyspnea, severe hypotension, and anaphylactic shock.1,6

The lack of either tranexamic acid or bovine aprotinin in EVICEL® eliminates the contraindication for use in contact with CSF or dura mater, and reduces the potential for hypersensitivity reactions to these agents. The principal difference between EVICEL® and CROSSEAL Fibrin Sealant is the absence of TA in EVICEL®.

EVICEL® was approved by the FDA in June 2006 on the basis of comparability to CROSSEAL Fibrin Sealant.
SUMMARY OF FEATURES

• Effectively achieves hemostasis during vascular surgery
• Human-derived protein
• Bovine-free formulation
• BAC2 (Human Fibrinogen Solution) component has been treated to remove plasminogen. Therefore, tranexamic acid is not required in BAC2 (Human Fibrinogen Solution).
• Not contraindicated for use in contact with cerebrospinal fluid or dura mater
• Double virus inactivation/removal
• Frozen liquid—no reconstitution necessary
• Less than 1-minute preparation time after thawing

• Clog-resistant triple lumen applicator tip—can be trimmed if necessary
• Same applicator can be used for dripping and spraying, no need to purchase extra accessories
• Needle-free system
• Convenient 1-mL, 2-mL, and 5-mL kits (total volume of 2.0 mL, 4.0 mL, and 10.0 mL, respectively)
• Preassembled delivery device—easy to use
• Can be refrigerated (2-8°C) for up to 30 days after thawing
• Unopened vials—stable at room temperature for up to 24 hours
• Clot transparency allows visualization of hemostasis and underlying tissue

Please see the Full Prescribing Information enclosed.

INDICATIONS

EVICEL® Fibrin Sealant (Human) is indicated as an adjunct to hemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

CONTRAINDICATIONS

Intravascular Application
Do not inject EVICEL® directly into the circulatory system. Intravascular application of EVICEL® may result in life-threatening thromboembolic events (see WARNINGS and PRECAUTIONS, Application Precautions (5.1) and ADVERSE REACTIONS, Post Marketing Experience (6.2)).

Hypersensitivity
Do not use EVICEL® in individuals known to have anaphylactic or severe systemic reaction to human blood products (see ADVERSE REACTIONS, Post Marketing Experience (6.2)).

Arterial Bleeding
Do not use EVICEL® for treatment of severe or brisk arterial bleeding. In these situations, EVICEL® will be washed away in the flow of blood before hemostasis can be attained.
Fibrin Sealants
Fibrin Sealants

HISTORY
The use of fibrin to facilitate hemostasis was reported for the first time in 1909 by Bergel.9 Because the fibrin was derived from circulating plasma concentrations of fibrinogen and thrombin, the quality of the resulting clot was poor. In the early 1940s, fibrin derived from the fractionation of plasma was used to “suture” human nerves, but the product was rapidly inactivated by fibrinolysis.10,11 In 1944, fibrinogen as citrated plasma was combined with thrombin to accelerate clot formation,12 and plasma-derived fibrinogen and thrombin were used to enhance the adherence of skin grafts.13 Highly concentrated fibrinogen precipitated from frozen plasma became available in the 1960s, and this cryoprecipitate was used in 1972 to perform nerve anastomoses.14 In 1975, the first reports of clinical applications of autologous fibrin sealant were published in Europe.15 In the 1980s, a two-component fibrin sealant consisting of human thrombin and highly concentrated human fibrinogen with enriched factor XIII (fibrin stabilizing factor) was introduced in Europe. This fibrin sealant was first used in pediatric surgery in 1981 to seal a ruptured spleen,16 and in 1982 during a partial spleen resection17 and for congenital esophageal malformations.18 The range of uses for fibrin sealant has expanded gradually since that time. However, because of concerns about the risk of transmission of blood-borne pathogens such as human immunodeficiency virus (HIV), the acceptance of fibrin sealants as an adjunct to hemostasis and for other surgical uses was slow in the US during the 1980s and early 1990s. Following the development of a proprietary virus inactivation process that destroyed most lipid-enveloped viruses including HIV, hepatitis B (HBV), and hepatitis C (HCV), blood-derived fibrin sealants were approved for marketing for the first time in the US in 1998 and have been used in a variety of clinical settings. Fibrin sealants have been used to seal tissue planes,19 to “glue” tissues together,20 to control postoperative bile leakage,21 and as a vehicle to deliver drugs.22 Eleftheriadis and Kotzampassi used a variety of fistuloscopic interventions to treat postoperative fistulas in 14 patients.19 Patients with high-output drainage required fibrin sealing in addition to other interventions. Tanaka et al found that fibrin glue sealing was effective in controlling bile leakage when the bile duct was not connected to the common bile duct following hepatic resection for malignant hepatic tumors in two patients.21

GENERAL DESCRIPTION
Fibrin sealants replicate the final phase of the coagulation cascade—the conversion of fibrinogen to fibrin by thrombin and the formation of an insoluble fibrin clot. Therefore, all fibrin sealants consist of a fibrinogen component and a thrombin component. Fibrin sealant may contain autologous fibrinogen (derived from the patient’s own plasma), which is typically combined with bovine thrombin, or heterologous components (produced from pooled human plasma). The fibrin clot that forms when the fibrinogen and thrombin components of fibrin sealant are mixed has all the properties of a “natural” fibrin clot, allowing fibrin sealants to be used as hemostatic agents to stop bleeding during surgery.23
USE OF FIBRIN SEALANTS IN LIVER SURGERY

The liver is highly vascular, and the cut surface is friable. Liver surgery can be hampered by the difficulty in controlling hemorrhage, particularly the slow oozing from injured hepatic surfaces. During surgery, bleeding can be persistent and difficult to control with standard hemostatic techniques such as suture ligation, conventional cautery, or argon beam coagulation with or without either partial or total vascular occlusion. Some patients undergoing liver surgery require 12 units or more of red blood cells to maintain a hemoglobin concentration of 10 g/dL.

One particularly important use of fibrin sealants is to control bleeding from the cut surface of the liver during hepatic surgery. Intraoperative blood loss during liver resection remains a major concern because it is associated with an increased rate of postoperative complications and decreased long-term survival. This has particular clinical relevance because the liver is also the primary site for the synthesis of most clotting factors. Patients with hepatic disorders requiring surgical intervention may not produce adequate quantities of these clotting factors and may thus be at increased risk of bleeding from the cut surface of the liver.

The most common operation performed on the liver is hepatic resection. Partial hepatic resection is generally accepted as the treatment of choice for primary liver cancer, with reported 5-year survival rates of up to 50%, although the criteria for resectability are met by fewer than 30% of patients. Postoperatively, patients may be exposed to complications related to bleeding and massive blood transfusion. Fibrin sealants applied to the undersurface of the diaphragm after hepatic resection may reduce the rate of left-sided pleural effusion, another complication of hepatectomy.

Liver transplantation is now performed selectively on some patients with widespread hepatic carcinoma who are not candidates for partial resection. In such patients, complete liver resection is performed. At the same time, a partial resection is performed on a living donor (live-donor liver transplantation). Fibrin sealants have been used to manage bleeding in both the donor and recipient sites.
USE OF FIBRIN SEALANTS IN VASCULAR SURGERY

Vascular surgery includes treatment of all vessels outside the heart in patients with disorders of the circulatory system. The traditional vascular surgical procedures include bypasses with vascular anastomoses and other reconstructions (particularly to repair aneurysms). In the past 2 decades, there have been numerous diagnostic and surgical technological advances in vascular surgery that have allowed endovascular and minimally invasive approaches in the treatment of vascular disorders, such as endovascular aneurysm repair, angioplasty, placement of stenting devices, and endoluminal bypasses.

Atherosclerosis is a commonly occurring disorder of the cardiovascular system that involves a gradual buildup of atherosclerotic plaque within the media (middle) and the intimal (inside) layers of the arterial wall, which eventually causes narrowing of the arterial lumen and restricts or obstructs blood flow. Occasionally, small pieces of the plaque or a clot can break off from the plaque, thus blocking smaller arteries and resulting in tissue ischemia and necrosis (such as stroke or myocardial infarction) if the ischemia persists.

One of the most common vascular procedures performed in patients with carotid artery disease is the carotid endarterectomy. The rationale for operating on those patients is to remove the plaque and restore blood flow in order to prevent brain ischemia and reduce the risk of stroke. After the atherosclerotic plaque is removed, the artery is usually closed using primary closure (ie, suturing) or patch angioplasty, using a vein patch or prosthetic material, such as polytetrafluoroethylene (PTFE) graft. For some patients, bleeding at the suture line may persist, which may increase intraoperative blood loss and extend the duration of surgery. In that case, the application of fibrin sealant as an adjunctive hemostatic agent could be beneficial. The efficacy of fibrin sealant has been investigated during carotid endarterectomy using PTFE patch closure in a prospective, randomized clinical study and demonstrated that application of fibrin sealant significantly (P<0.001) decreased the time to hemostasis compared with standard hemostatic measures. The application of fibrin sealant after carotid endarterectomy is illustrated in Figure 1. Note: Fibrin sealants should not be used to manage brisk arterial bleeding.

![Figure 1. Application of fibrin sealant to the suture line during carotid endarterectomy.](image)
Another arterial disorder is an aortic aneurysm, which occurs when a wall of the thoracic or abdominal aorta (or other artery) is weakened and bulges as a result of structural protein abnormalities, medial degeneration, or plaque buildup and subsequent damage to the underlying vessel wall. Abdominal aortic aneurysms are more common than thoracic aortic aneurysms. Abdominal aortic aneurysms are typically asymptomatic and are detected on an incidental abdominal radiograph, computed tomography (CT) scan, or other imaging procedure. However, in some patients the aneurysm may rupture before diagnosis or intervention and result in excessive bleeding. Aneurysms that are larger than 5.5 cm in diameter or that grow more than 0.6-0.8 cm per year require elective surgical intervention. The mortality rate of ruptured aneurysms requiring surgery is approximately 80%, which corresponds to 9,000 deaths per year in the United States. Currently, the annual number of elective unruptured aneurysm repairs is approximately 40,000 patients in the United States. Surgical repair of an abdominal aortic aneurysm typically involves replacement of the portion of damaged aorta with a synthetic graft. During the surgery, bleeding may persist along the suture line of the anastomotic sites where the aorta and vascular graft are joined and, therefore, the application of fibrin sealant to these bleeding sites (Figure 2) may be beneficial for decreasing the time required to achieve hemostasis.

Figure 2. Application of fibrin sealant to achieve hemostasis at an anastomotic site during repair of an abdominal aortic aneurysm.
One of the most common cardiovascular procedures is the coronary artery bypass graft (CABG), which is performed to bypass arteries in the heart that are blocked or clogged with plaque. This procedure is performed for approximately 800,000 patients in the world each year to treat myocardial ischemia. Uncommonly, emergency CABG is performed because of failed percutaneous transcoronary angioplasty (PTCA). During the CABG surgery, one end of a grafted vessel (generally a saphenous vein harvested from the leg or a radial artery removed from the arm) is joined to the coronary artery beyond the site of the blockage, while the other end of the vessel is joined to the aorta. In addition (or alternatively), one end of an internal mammary artery may be directly anastomosed to a coronary artery distal to the site of blockage. Using this method, blood flow is re-routed to bypass the blockage in the coronary artery.

Fibrin sealants have been used to manage bleeding in cardiac surgery in a number of areas, such as: 1) Mediastinal soft tissue; 2) Internal Mammary Artery (IMA) bed; and 3) Graft sites. Vascular reconstructions are also performed during organ transplantation procedures, which require anastomoses of existing blood vessels to those associated with donor organs. As with other vascular procedures, achieving hemostasis during and following the organ transplant is critical for the success of the procedure.

The current description of selected vascular procedures provides an example of surgical situations that may require vascular anastomosis or reconstruction. The use of EVICEL® can be beneficial during such vascular procedures as an adjunctive measure in achieving hemostasis.

THE USE OF FIBRIN SEALANTS IN RETROPERITONEAL AND INTRA-ABDOMINAL SURGERY

The retroperitoneum is the anatomical space behind the peritoneum, which is the serous membrane that surrounds the viscera in the abdominal cavity. Structures that lie in this space are termed “retroperitoneal,” and include the kidneys, all but the first few centimeters of the duodenum, adrenal glands, ureters, aorta, inferior vena cava, and the middle third of the rectum. The intra-abdominal space (or peritoneal cavity) is the largest hollow space in the body, extending from the diaphragm to the top of the pelvic cavity, and is surrounded by the spine and abdominal muscles. It contains most of the alimentary tract, liver, pancreas, spleen, kidneys, and adrenal glands.

Retroperitoneal and intra-abdominal surgical procedures may be performed within multiple specialties, such as general, urologic and gynecologic surgery. These procedures are frequently utilized in urologic practice to address conditions affecting the kidneys, ureters, bladder, and retroperitoneal lymph nodes. Common gynecologic procedures that are performed within the retroperitoneum or intra-abdominal space include radical hysterectomy, pelvic and para-aortic lymphadenectomy, and uterine artery occlusion, while common urologic retroperitoneal procedures include nephrectomy, ureteral surgery, pyeloplasty, and retroperitoneal lymph node dissection. General surgical procedures include tumor debulking, colectomy, cholecystectomy, cystectomy, pancreatectomy, splenectomy, and gastrectomy, among others. Although many procedures can now be performed laparoscopically, such
procedures may be complicated by bleeding, and the attainment of hemostasis is often challenging when using advanced laparoscopic suturing techniques.\textsuperscript{41}

The efficacy and safety of EVICEL\textsuperscript{®} in mild to moderate bleeding in soft tissues during non-emergent retroperitoneal and intra-abdominal surgery were recently evaluated in a prospective, randomized, controlled evaluation. A wide range of surgery types were included, ranging from hysterectomy, prostatectomy, and nephrectomy to tumor debulking, colectomy, cholecystectomy, cystectomy, pancreatectomy, splenectomy, and gastrectomy. In that trial, fibrin sealant use effectively facilitated hemostasis, with a greater proportion of patients treated with fibrin sealant versus an absorbable hemostat achieving hemostasis within 10 minutes (see the Clinical Studies section for details). Those data were submitted to the US Food and Drug Administration (FDA) to support a general hemostasis indication which requires safety and efficacy data in a variety of surgical settings. Previously submitted trials have demonstrated the efficacy and safety of this fibrin sealant in vascular surgery and in liver surgery.\textsuperscript{42} (This latter trial\textsuperscript{42} assessed the hemostatic efficacy and safety of the predecessor of EVICEL\textsuperscript{®}, CROSSEAL\textsuperscript{®} Fibrin Sealant [Human]). QUIXIL\textsuperscript{®}, the European equivalent of CROSSEAL Fibrin Sealant, has also demonstrated hemostatic effects in the orthopedic surgical setting.\textsuperscript{43,44}
Clinical Pharmacology
Clinical Pharmacology

MECHANISM OF ACTION

The mechanism of blood coagulation in vivo can be simplified to 3 essential steps: 1) A complex of substances collectively called prothrombin activator is formed in response to vascular injury; 2) The prothrombin activator catalyzes the conversion of prothrombin into thrombin; and 3) The thrombin acts as an enzyme to convert fibrinogen into fibrin monomers which polymerize to form fibrin strands that enmesh platelets, blood cells, and plasma to form the clot itself.45

Fibrinogen (factor I), a high molecular weight glycoprotein that occurs naturally in plasma in quantities of 100 to 700 mg/dL, is the active ingredient in BAC2 (Human Fibrinogen Solution). Fibrinogen consists of three pairs of polypeptides—A-α, B-β, and γ-γ—that form 6 chains, covalently linked near their N-terminals through disulfide bonds.46 Short polypeptide sequences at the amino terminals of the A-α and B-β chains comprise fibrinopeptides A and B, respectively. The fibrinopeptide regions of fibrinogen contain several glutamate and aspartate residues, which impart a high negative charge to this region and aid in the solubility of fibrinogen in plasma.

Thrombin, a protease, cleaves the fibrinogen molecule enzymatically at four arginine-glycine bonds between fibrinopeptides A and B and the remainder of the A-α and B-β chains (Figure 3).44 Release of the fibrinopeptides of the fibrinogen molecule generates individual fibrin molecules, or monomers. These soluble monomers spontaneously aggregate and polymerize within seconds in a regular array via noncovalent bonding, forming insoluble fibrin polymer strands that are not cross-linked with each other, which results in a relatively weak fibrin clot.
Figure 3. Formation of the stable fibrin clot. Thrombin cleaves fibrinopeptides A (●) and B (●), which are covalently linked through disulfide bonds (→), from fibrinogen to form fibrin monomers. These fibrin monomers spontaneously polymerize within seconds via noncovalent hydrogen bonds (↔) forming soluble fibrin polymers, which are not cross-linked with each other and which form a relatively weak clot. Activated factor XIII (FXIIIa), in the presence of calcium, then catalyzes the formation of covalent bonds (▼) between adjacent soluble fibrin polymers, creating insoluble fibrin polymers (the stable fibrin clot), thereby adding tremendously to the three-dimensional strength of the fibrin meshwork.

In addition to transforming fibrinogen to fibrin, thrombin also converts factor XIII (fibrin stabilizing factor) to activated factor XIII (factor XIIIa), a highly specific transglutaminase that, in the presence of calcium, catalyzes the formation of covalent bonds between the fibrin monomers and multiple cross-linkages between the adjacent fibrin strands, thereby adding tremendously to the three-dimensional strength of the fibrin meshwork. Factor XIII, which is present in plasma and tissues, not only cross-links fibrin to itself but also to the tissue, anchoring the clot firmly to the wound (Figure 4).
Figure 4. Formation of a natural fibrin clot, with trapped red blood cells. The clot produced by commercial fibrin sealants is never identical to a plasmatic clot for the following reasons: 1) Concentration of fibrinogen is about 30 times higher than in blood; 2) Concentration of thrombin is also very high; and 3) The fibrin clot of fibrin sealant rarely entraps blood components. (Provided by Dennis Kunkel Microscopy, Inc.)

EVICEL® functions independent of the body’s coagulation mechanism (Figure 5). In a randomized controlled trial involving vascular surgery, EVICEL® demonstrated safety and efficacy. The large majority of these patients were anticoagulated with heparin. The fibrin clot is resorbed during normal wound healing within days to weeks of EVICEL® application, depending on the type of surgery, proteolytic activity at the treated site, and the amount of EVICEL® used.

Figure 5. Steps in the formation of a fibrin clot produced by EVICEL®.
CONTENTS
The BAC2 (Human Fibrinogen Solution) and thrombin components of EVICEL® Fibrin Sealant (Human) appear as white to slightly yellowish opaque masses when frozen and as clear to slightly opalescent and colorless to slightly yellowish solutions, when thawed. The components contain no preservatives.

BAC2 (Human Fibrinogen Solution) is a concentrated solution of clottable plasma proteins, consisting mainly of fibrinogen. Thawed BAC2 (Human Fibrinogen Solution) is a sterile solution with a pH range of 6.7 to 7.2 and consists mainly of a concentrate of human fibrinogen (factor I). Fibrinogen is a protein from human blood that forms a clot when combined with thrombin. The composition of the BAC2 (Human Fibrinogen Solution) solution is:

**ACTIVE INGREDIENT:**
Concentrate of human fibrinogen (55-85 mg/mL)

**OTHER INGREDIENTS:**
Arginine hydrochloride
Glycine
Sodium chloride
Sodium citrate
Calcium chloride
Water for injection

Thrombin is a highly specific protease that transforms the fibrinogen in BAC2 (Human Fibrinogen Solution) into fibrin. Thawed thrombin is a sterile solution with a pH range of 6.8 to 7.2 that contains highly purified human thrombin and calcium chloride for activation of clotting of the final, combined product. The composition of the thrombin solution is:

**ACTIVE INGREDIENT:**
Purified active human thrombin (800-1200 IU/mL)

**OTHER INGREDIENTS:**
Calcium chloride
Human albumin
Mannitol
Sodium acetate
Water for injection

In contrast to fibrin sealants that contain bovine-derived protein such as bovine aprotinin (an antifibrinolytic) or bovine thrombin, EVICEL® contains only human-derived protein. Therefore, it does not present a risk of allergic reactions to cross-species foreign protein. Anaphylactic reactions may occur in rare cases. No adverse events of this type were reported in the conduct of the clinical trials.
PRODUCTION

Cryoprecipitate, the starting material for BAC2 (Human Fibrinogen Solution), and cryoprecipitate-poor plasma, the starting material for the production of thrombin, are made from pooled human plasma obtained from US licensed plasma or blood collection centers. The plasma is collected from carefully screened donors and is deep-frozen. Samples of donated plasma are tested for viral contamination. Frozen plasma is then thawed at 1°C to 6°C and centrifuged to separate the insoluble cryoprecipitate from the cryoprecipitate-poor plasma supernatant.

The following flow chart summarizes the production process.
**BIOLOGICAL ACTIVE COMPONENT 2**

The cryoprecipitate is solubilized in citrated glycine buffer and treated with aluminum hydroxide gel to adsorb and precipitate the vitamin K-dependent clotting factors—prothrombin (factor II), factor VII, factor IX, and factor X—which are then removed by centrifugation followed by filtration. The remaining solution is incubated for 4 hours at 30°C with a solvent detergent (SD) mixture consisting of 1% tri-n-butyl phosphate and 1% Triton X-100 for inactivation of lipid-enveloped viruses such as HIV, HBV, and HCV (first virus inactivation step). This first step of virus inactivation has been validated to show that pH, temperature, and SD reagent concentration remain uniform throughout the 4-hour incubation process.

The SD method of virus inactivation has also been validated with respect to virus killing and protein compatibility. SD-treated products provide a high margin of safety with regard to all major blood-borne viruses, including HIV, HBV, and HCV. The high specificity of reaction is derived from its mechanism of action being directed against the lipid coat of enveloped viruses.

The SD reagents are removed by castor oil extraction and reverse phase chromatography (C-18 column). Sucrose (1.8 g/g column filtrate) and glycine (0.11 g/g) are then added as stabilizers, the mixture is warmed to 37°C under stirring, and the pH is adjusted, if necessary, to 6.9-7.1. The solution is then treated by pasteurization (second virus inactivation step) by heating to 60 ± 0.5°C and is maintained at that temperature for 10 hours. Pasteurization reduces the possibility of infectivity by non–lipid-enveloped viruses such as hepatitis A (HAV) as well as lipid-enveloped viruses.

After pasteurization, the stabilizers used during heat treatment are removed by diafiltration, and the product is partially concentrated by ultrafiltration. Plasminogen is removed by affinity chromatography on Tranexamic acid-Sepharose and further concentrated by a final ultrafiltration step.

The BAC2 (Human Fibrinogen Solution) solution is filter sterilized and 1, 2, or 5 mL vials are filled aseptically with the BAC2 (Human Fibrinogen Solution) sterile bulk product, frozen at -60°C, and stored at -30 ± 5°C until distribution.

**THROMBIN**

The cryoprecipitate-poor plasma is applied to an anionic column for binding of prothrombin and activation to thrombin. Thrombin is generated by the addition of calcium chloride to the anionic resin. The resultant thrombin does not bind to the column and is eluted with calcium chloride. Thrombin undergoes SD treatment for 6 hours at 26 ± 1°C. As with BAC2 (Human Fibrinogen Solution), this first step of virus inactivation has been validated to show that pH, temperature, and SD reagent concentration remain uniform throughout the 6-hour incubation process.

The SD reagents are removed by cationic chromatography (SP-Toyopearl). Mannitol (as a 15% solution) and human albumin are added to the product as stabilizers to a final concentration of 2% (w/w) and 0.2% (w/w), respectively. The stabilized solution is then nanofiltered through
a Viresolve® 70 ultrafiltration module with the use of sodium acetate buffer (containing 2% [w/w] mannitol and 0.2% [w/w] human albumin) to rinse the membrane. This is the second virus removal step. Apart from a validated removal of lipid-coated viruses, this second viral removal step removes all the known nonlipid-coated viruses including parvovirus. The filtrate is formulated with calcium chloride to 40 mM and the concentration of human albumin readjusted to 0.6% if required.

The thrombin solution is sterile filtered and 1, 2, or 5 mL vials are filled aseptically with the thrombin sterile bulk product, frozen at -60°C, and stored at -30 ± 5°C until distribution.

Although the BAC2 (Human Fibrinogen Solution) and thrombin components undergo two distinct, independent virus inactivation/removal steps shown to be capable of significant viral reduction, as with all plasma-derived products, no procedure has been shown to be completely effective in removing viral infectivity from derivatives of human plasma. (See Full Prescribing Information.)

**PHARMACOKINETICS AND PHARMACODYNAMICS**

Thrombin is partly adsorbed by the formed fibrin, and any excess thrombin is inactivated by protease inhibitors in the blood. In a study to evaluate the blood levels of 125I-radiolabeled thrombin after application of CROSSEAL® Fibrin Sealant (Human) to hepatic wounds in rabbits, it was determined that excess thrombin is quickly complexed with anti-thrombin, and its total inactivation and elimination are rapid. The study results verified that systemic exposure to the thrombin component of fibrin sealant is approximately equal to systemic exposure to thrombin generated by a minor hemorrhage and poses no increased risk of intra-vascular clotting and thromboembolism.
**Viral Safety**

**DONOR SCREENING**

Potential donors are screened for general health and possible risk factors before donating plasma. Each individual plasma unit obtained for production of EVICEL® is tested according to FDA regulations (21 CFR 610.40) and memoranda concerning testing of individual donation units for HBV surface antigen (HBsAg), HIV-1 and -2 antibodies (HIV-1/2 Ab), and HCV antibody (HCV Ab).

**NUCLEIC ACID TESTING**

The plasma used in the manufacture of EVICEL® has undergone nucleic acid testing (NAT in mini-pools) with the use of polymerase chain-reaction technology and has been found negative for HAV, HBV, HCV, and HIV-1. Although NAT for HCV and HIV-1 is approved by the FDA, investigational testing is still being performed for HAV and HBV to determine the effectiveness of NAT to detect low levels of viral material early in the “window period” of infectivity. The significance of a negative result for these viruses is unknown since the effectiveness of the test has not been established.

Nucleic acid testing for parvovirus B19 is also performed. To restrict the viral load of parvovirus B19 in the starting plasma pool, the level of contamination is not permitted to exceed 10,000 copies/mL.

**VIRUS INACTIVATION/REMOVAL**

The manufacturing procedure for EVICEL® includes processing steps designed to reduce the risk of viral transmission. As noted previously, both BAC2 (Human Fibrinogen Solution) and thrombin undergo 2 discrete virus inactivation/removal steps, which are summarized in Table 1.

<table>
<thead>
<tr>
<th>Step</th>
<th>Component</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>BAC2 (Human Fibrinogen Solution)</td>
</tr>
<tr>
<td></td>
<td>Solvent detergent treatment (1% tri-n-butyl phosphate, 1% Triton X-100) for 4 hours at 30°C</td>
</tr>
<tr>
<td>2</td>
<td>Pasteurization (10 hours at 60°C)</td>
</tr>
</tbody>
</table>
Solvent detergent treatment, used in Step 1, is well established as a highly efficient method of inactivating lipid-enveloped viruses in plasma derivative products without affecting the biologic activity of plasma proteins.\textsuperscript{55,56}

Pasteurization and nanofiltration, used in Step 2, are nonspecific virus inactivation and removal techniques, respectively, reducing the risk of transmission of non–lipid-enveloped viruses and adding an extra margin of safety to the inactivation of lipid-enveloped viruses. Heat treatment during pasteurization inactivates lipid-enveloped and non–lipid-enveloped viruses in BAC2 (Human Fibrinogen Solution). Nanofiltration, which uses a membrane with an average pore size of 28 nm, removes lipid-enveloped and non–lipid-enveloped viruses from thrombin. Viral validation studies indicate that even parvovirus, one of the smallest human viral agents, is significantly removed by the nanofiltration step.

The efficacy of SD treatment and pasteurization in inactivating a range of viruses has been assessed in CROSSEAL* Fibrin Sealant (Human) validation studies. The validated process steps are designed to reduce the risk of viral transmission in conjunction with plasma screening. In addition to the screening processes described above, each manufacturing pool is tested for HBsAg, HIV-1/2, HCV by NAT and for Parvovirus B19 by NAT. Manufacturing pool testing, however, is of a lower sensitivity than the individual unit testing.

The viruses used for the validation studies were selected to give a range of physicochemical characteristics. These viruses are listed and their characteristics summarized in Table 2.
Table 2. Viruses Used in CROSSEAL® Fibrin Sealant (Human) Validation Studies

<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Genus</th>
<th>Genome</th>
<th>Lipid envelope</th>
<th>Size (nm)</th>
<th>Resistance to physicochemical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus-1</td>
<td>Retro</td>
<td>Lentivirus</td>
<td>RNA</td>
<td>Yes</td>
<td>80-130</td>
<td>Low</td>
</tr>
<tr>
<td>Sindbis virus</td>
<td>Toga</td>
<td>Alphavirus</td>
<td>RNA</td>
<td>Yes</td>
<td>60-70</td>
<td>Low</td>
</tr>
<tr>
<td>Bovine viral diarrhea virus</td>
<td>Flavi</td>
<td>Pestivirus</td>
<td>RNA</td>
<td>Yes</td>
<td>60-70</td>
<td>Low</td>
</tr>
<tr>
<td>Pseudorabies virus</td>
<td>Herpes</td>
<td>Varicellovirus</td>
<td>DNA</td>
<td>Yes</td>
<td>150-200</td>
<td>Medium</td>
</tr>
<tr>
<td>Encephalomyocarditis virus</td>
<td>Picorna</td>
<td>Cardiovirus</td>
<td>RNA</td>
<td>No</td>
<td>28-30</td>
<td>Medium</td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>Picorna</td>
<td>Hepatovirus</td>
<td>RNA</td>
<td>No</td>
<td>28-30</td>
<td>High</td>
</tr>
<tr>
<td>Canine parvovirus</td>
<td>Parvo</td>
<td>Parvovirus</td>
<td>DNA</td>
<td>No</td>
<td>18-26</td>
<td>Very high</td>
</tr>
</tbody>
</table>

1 HIV-1 is classified under the Retrovirus family, Lentivirus genus. It is recommended in the Committee for Proprietary Medicinal Products Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95) to be used directly in validation studies. It also serves as a model for HIV-2.

2 Sindbis virus is an RNA negative-strand, lipid-enveloped virus of the Togavirus family, Alphavirus genus that serves as a model for HCV. It is not possible to study HCV directly, because it cannot be propagated. Sindbis virus has been used to demonstrate the efficacy of solvents and nonionic detergents such as tri-n-butyl phosphate/Triton X-100 to break down the lipid-envelope structure of the virus.

3 Bovine viral diarrhea virus (BVDV) is an RNA positive-strand, lipid-enveloped virus of the Flaviviridae family, Pestivirus genus. Because HCV is also a member of this family, BVDV is regarded as a good model for HCV.

4 Pseudorabies virus is classified under the Herpesvirus family, Varicellovirusae genus. It can serve as a model for human bloodborne herpes viruses such as Epstein-Barr virus, cytomegalovirus, and human herpesvirus 6, since all herpes viruses have a similar structure and are indistinguishable morphologically. Pseudorabies virus can also serve as a model for other DNA lipid-enveloped viruses and is particularly suitable for viral spiking studies, as it can be obtained in high titers and an accurate quantitative plaque assay is available.

5 Encephalomyocarditis virus is classified under the Picornavirus family, Cardiovirus genus. It can be considered a model for hepatitis A virus, which is also in the Picornavirus family and is of the same size.

6 Hepatitis A virus (HAV) is a small non–lipid-enveloped virus that may be transmitted by blood products. It is therefore considered to be a relevant virus.

7 Canine parvovirus is a DNA positive-strand, non–lipid-enveloped virus, which is resistant to chemical treatment. It can be considered a model for human parvovirus B19 on the basis of its similar morphology and structure. This model virus has been used as a negative control for the solvent detergent virus inactivation step and to determine the effectiveness of the other virus inactivation/removal steps in eliminating non–lipid-enveloped viruses.
The results of process virus inactivation validation studies are summarized in Table 3 for BAC2 (Human Fibrinogen Solution) and in Table 4 for thrombin.

**Table 3. Results of Process Virus Inactivation Studies for Biological Active Component 2**

<table>
<thead>
<tr>
<th></th>
<th>HIV-1</th>
<th>BVDV</th>
<th>PRV</th>
<th>EMCV</th>
<th>HAV</th>
<th>CPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction factor (log_{10})</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvent detergent treatment</td>
<td>&gt;4.42</td>
<td>&gt;4.39</td>
<td>&gt;3.96</td>
<td>Not done</td>
<td>Not done</td>
<td>0.0</td>
</tr>
<tr>
<td>Pasteurization</td>
<td>&gt;4.39</td>
<td>&gt;5.46</td>
<td>Not done</td>
<td>3.69</td>
<td>&gt;5.78</td>
<td>1.33</td>
</tr>
<tr>
<td>Global reduction factor</td>
<td>&gt;8.81</td>
<td>&gt;9.85</td>
<td>&gt;3.96</td>
<td>3.69</td>
<td>&gt;5.78</td>
<td>1.33</td>
</tr>
</tbody>
</table>

HIV-1, human immunodeficiency virus-1; BVDV, bovine viral diarrhea virus; PRV, pseudorabies virus; EMCV, encephalomyocarditis virus; HAV, hepatitis A virus; CPV, canine parvovirus.

**Table 4. Results of Process Virus Inactivation Studies for Thrombin**

<table>
<thead>
<tr>
<th></th>
<th>HIV-1</th>
<th>SBV</th>
<th>BVDV</th>
<th>PRV</th>
<th>EMCV</th>
<th>HAV</th>
<th>CPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reduction factor (log_{10})</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solvent detergent treatment</td>
<td>&gt;5.82</td>
<td>&gt;5.31</td>
<td>&gt;4.74</td>
<td>&gt;4.25</td>
<td>Not done</td>
<td>Not done</td>
<td>0.0</td>
</tr>
<tr>
<td>Nanofiltration †</td>
<td>&gt;4.36</td>
<td>&gt;5.32</td>
<td>Not done</td>
<td>&gt;5.47</td>
<td>6.37</td>
<td>6.95</td>
<td>5.85</td>
</tr>
<tr>
<td>Global reduction factor</td>
<td>&gt;10.18</td>
<td>&gt;10.63</td>
<td>&gt;4.74</td>
<td>&gt;9.72</td>
<td>6.37</td>
<td>6.95</td>
<td>5.85</td>
</tr>
</tbody>
</table>

† Average pore size is 28 nm.
HIV-1, human immunodeficiency virus-1; SBV, Sindbis virus; BVDV, bovine viral diarrhea virus; PRV, pseudorabies virus; EMCV, encephalomyocarditis virus; HAV, hepatitis A virus; CPV, canine parvovirus.
Clinical Studies

As previously mentioned, EVICEL® is a new version of a previously available fibrin sealant called CROSSEAL® Fibrin Sealant (Human). CROSSEAL Fibrin Sealant received FDA approval in the United States in March 2003. EVICEL® is introduced to offer a fibrin sealant with the same features and benefits as CROSSEAL Fibrin Sealant, but without the need for an antifibrinolytic agent to ensure its stability.

CROSSEAL Fibrin Sealant containing tranexamic acid, an antifibrinolytic agent commonly used in the formulation of fibrin sealants, is contraindicated for use in contact with cerebral spinal fluid (CSF) or dura mater. Bovine aprotinin, another commonly used antifibrinolytic agent, can cause severe allergic or anaphylactic reactions. The lack of either tranexamic acid or bovine aprotinin in EVICEL® eliminates the contraindication for use in contact with CSF or dura mater, and greatly reduces the potential for hypersensitivity reactions.

The principal difference between EVICEL® and CROSSEAL Fibrin Sealant is the absence of tranexamic acid in EVICEL®.

The clinical studies summarized in this section were conducted with CROSSEAL Fibrin Sealant on patients undergoing liver resection. The findings of these clinical studies are equally applicable to EVICEL®, since EVICEL® is essentially a new version of the CROSSEAL Fibrin Sealant.

SINGLE-BLIND STUDY OF SAFETY AND EFFICACY IN REDUCING TIME REQUIRED TO ACHIEVE HEMOSTASIS

CROSSEAL Fibrin Sealant was compared with FDA-licensed topical hemostatic agents in a pivotal Phase III, single-blind, randomized, parallel-group study in 121 patients undergoing liver resection at 15 centers. The study was designed to assess the efficacy of a single CROSSEAL Fibrin Sealant kit with that of an unlimited quantity of comparative hemostatic agents in reducing the time to hemostasis. Hemostatic agents in the control group were AVITENE® (CR Bard), GELFOAM® (Pharmacia), OXYCEL® (Desert), SURGICEL® Absorbable Hemostat and SURGICEL® NU-KNIT® Absorbable Hemostat (ETHICON), THROMBINAR® (genTrac), and ACTIFOAM® (CR Bard). Secondary efficacy endpoints included a comparison of the treatment groups with respect to intraoperative blood loss from the time of application to abdominal closure, the duration of postoperative bile loss until the time of drain removal, and the occurrence of postoperative abdominal fluid collections. Safety assessment included analysis of adverse events occurring up to 6 weeks after surgery. Patients were randomized to CROSSEAL Fibrin Sealant or a comparative agent at the conclusion of liver resection surgery if bleeding from the cut surface of the liver could not be controlled by standard methods. Fifty-eight patients were randomized to the CROSSEAL Fibrin Sealant group and 63 to the control group. The results are summarized in Table 5.
Table 5. Efficacy of CROSSEAL® Fibrin Sealant in a Study Assessing Time to Hemostasis

<table>
<thead>
<tr>
<th>Time to hemostasis (minutes)</th>
<th>CROSSEAL Fibrin Sealant</th>
<th>CONTROL</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to hemostasis (minutes)</td>
<td>5.3</td>
<td>7.7</td>
<td>0.011¹</td>
</tr>
<tr>
<td>Patients with abdominal fluid collection (%)</td>
<td>3.4</td>
<td>14.3</td>
<td>0.037</td>
</tr>
<tr>
<td>Patients with adverse events (%)</td>
<td>17.2</td>
<td>36.5</td>
<td>0.014</td>
</tr>
</tbody>
</table>

¹Intent-to-treat analysis, 1-sided.

The time to hemostasis was significantly shorter in the CROSSEAL Fibrin Sealant group than in the control group (5.3 minutes vs 7.7 minutes; 1-sided, P=0.011; 2-sided, P=0.022). In addition, the proportion of patients achieving hemostasis within 10 minutes was significantly greater in the CROSSEAL Fibrin Sealant group (91.4%) than in the control group (69.8%) (P=0.003, 2-sided).

The percentage of patients achieving hemostasis by time interval is shown below (Figure 6). The percentage of patients achieving hemostasis within 10 minutes was significantly higher in the CROSSEAL Fibrin Sealant group (91.4%) than in the control group (69.8%, 2-sided P=0.003).

Figure 6. Percentage of patients achieving hemostasis by treatment group and time interval.

The percentage of patients achieving hemostasis within 10 minutes was significantly higher in the CROSSEAL Fibrin Sealant group (91.4%) than in the control group (69.8%, 2-sided P=0.003).
Intra-abdominal blood loss, duration of surgery, postoperative decrease in hemoglobin and hematocrit, duration of blood loss in drainage fluid, and the number of blood transfusions did not differ significantly between the groups. However, compared with the control group, the CROSSEAL* Fibrin Sealant (Human) group had a significantly smaller proportion of patients with abdominal collections (14.3% vs 3.4%, \( P=0.037 \)) and a smaller proportion of patients with complications (36.5% vs 17.2%, \( P=0.014 \)).

Study center effects are to be expected in multicenter trials, particularly for surgical indications. Data from one center, which used a specific control agent, made a major contribution to the results. However, of the 16 surgeons who treated more than one patient in this study, 10 found the time to hemostasis to be equivalent to or shorter than that achieved with the specific control agent used.

**CONCLUSION**

Compared with the use of standard topical hemostatic agents, CROSSEAL Fibrin Sealant significantly reduced the time to achieve hemostasis following liver resection. Patients treated with the new fibrin sealant also experienced significantly fewer postoperative complications.

**OPEN-LABEL UNCONTROLLED STUDY TO ASSESS SAFETY AND EFFICACY**

CROSSEAL Fibrin Sealant was assessed in an open-label uncontrolled Phase II study in 21 patients undergoing liver resection or reduced-size liver transplantation. Efficacy parameters included intraoperative and postoperative blood loss and quality of hemostasis. A single application of CROSSEAL Fibrin Sealant in conjunction with standard hemostatic techniques was sufficient to prevent bleeding and promote hemostasis in more than 95% of patients.

**A PHASE III, MULTICENTER, PARALLEL-GROUP STUDY OF THE HEMOSTATIC EFFECTIVENESS AND SAFETY OF EVICEL® DURING VASCULAR SURGERY**

The hemostatic effectiveness and safety of EVICEL® versus manual compression during vascular surgical procedures using polytetrafluoroethylene (PTFE) graft material on an end-to-side femoral or upper extremity arterial anastomosis were evaluated in a Phase III, multicenter, randomized, parallel-group study. The study enrolled 127 patients at 16 centers in the United States and the United Kingdom. Patients who required adjunctive hemostatic measures at the suture line of the study anastomotic site (SAS) were randomized to receive EVICEL® or manual compression. The primary endpoint of the study was the absence of bleeding at the SAS at 4 minutes following randomization. Secondary effectiveness endpoints included the absence of bleeding at the SAS at 7 and 10 minutes following randomization, the incidence of treatment failure (defined as the presence of bleeding at the SAS at 10 minutes or the requirement for additional hemostatic measures during the initial 10-minute treatment period), and the incidence of complications that were potentially related to bleeding. Adverse events were also recorded.
A total of 127 patients were randomized to receive EVICEL® Fibrin Sealant (Human) (n = 75) or manual compression (n = 72). A significantly higher percentage of patients who received EVICEL® versus manual compression achieved hemostasis at the SAS at 4 minutes (85.3% vs 38.9%, respectively; ratio of the proportions of success = 11.3; 95% confidence interval [CI] for the ratio of the proportions of success, 4.7-27.5; \( P < 0.001 \)) (Figure 7). Significantly higher percentages of patients who received EVICEL® had also achieved hemostasis at the 7-minute (ratio of the proportions of success = 7.9; 95% CI for the ratio of the proportions of success, 2.8-21.9; \( P < 0.001 \)) and 10-minute (ratio of the proportions of success = 18.5; 95% CI for the ratio of the proportions of success, 3.7-91.8; \( P < 0.001 \)) time points compared with patients who received manual compression (Figure 7).

![Bar chart showing percentages of patients achieving hemostasis](image)

**Figure 7.** Percentages of patients in each treatment group that achieved hemostasis at each time point. A significantly higher percentage of patients who received EVICEL® versus manual compression achieved hemostasis at 4 minutes following randomization.

Results of additional effectiveness endpoints are provided in Table 6. A significantly lower incidence of treatment failure was observed for patients who received EVICEL® versus manual compression (8.0% vs 31.9%, respectively; ratio of the proportions of success = 0.14; 95% CI for the ratio of the proportions of success, 0.05-0.45; \( P < 0.001 \)). The incidence of complications that were potentially related to bleeding was similar between the treatment groups (95% CI for the ratio, 0.6-3.7; \( P = 0.426 \)), and a total of 64.0% of patients who received EVICEL® experienced at least 1 adverse event compared with 70.8% of patients who received manual compression.
Table 6. Hemostatic Effectiveness of EVICEL® During Vascular Surgical Procedures Using PFTE Grafts

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EVICEL® (n = 75), n (%)</th>
<th>Manual compression (n = 72), n (%)</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>6 (8.0%)</td>
<td>23 (31.9%)</td>
<td>0.18</td>
<td>0.07-0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complications potentially related to bleeding</td>
<td>12 (16.0%)</td>
<td>15 (20.8%)</td>
<td>1.5</td>
<td>0.6-3.7</td>
<td>0.426</td>
</tr>
</tbody>
</table>

PFTE, polytetrafluorethylene; CI, confidence interval.

CONCLUSION

A significantly higher percentage of patients who received EVICEL® versus manual compression during vascular surgery achieved hemostasis within 4 minutes following randomization. Results of this study demonstrate that EVICEL® is safe and effective for achieving hemostasis during vascular procedures using PFTE.

THE SAFETY AND EFFECTIVENESS OF EVICEL® COMPARED WITH AN ABSORBABLE HEMOSTAT FOR ACHIEVING HEMOSTASIS IN SOFT TISSUE DURING RETROPERITONEAL OR INTRA-ABDOMINAL SURGERY: A PROSPECTIVE RANDOMIZED TRIAL

The hemostatic effectiveness and safety of EVICEL® versus an absorbable hemostat in soft tissue during non-emergent retroperitoneal or intra-abdominal surgery were evaluated in a Phase III, randomized, active-controlled, multicenter study. The study enrolled 135 patients at 16 centers in the United States. Patients who experienced soft-tissue bleeding as a result of dissection at the site of the primary operative intent for which conventional surgical hemostatic techniques were considered impractical or ineffective were randomized to receive either EVICEL® (n = 66) or an absorbable oxidized regenerated cellulose hemostat (SURGICEL® Absorbable Hemostat, Johnson & Johnson Wound Management, a Division of Ethicon, Inc., Somerville, NJ) (n = 69) as an adjunct for hemostasis. Eleven pediatric patients (fibrin sealant, n = 4; absorbable hemostat, n = 7) were included in the overall population. The primary effectiveness endpoint was the hemostasis outcome at 10 minutes, with success defined as the absence of bleeding and no need for treatment with additional hemostatic measures. Secondary effectiveness endpoints included the hemostasis outcome at 4 and 7 minutes, the incidence of any complications that were potentially related to bleeding from the time of randomization to follow-up (7 to 14 days following the procedure), and the incidence of treatment failures (defined as the presence of bleeding at the target bleeding site 10 minutes post-randomization or brisk bleeding that required the use of additional hemostatic measures during the 10-minute observation period). The absolute time to hemostasis (TTH) was also recorded for each patient. Adverse events were recorded as they were reported from the time of randomization to the time of follow-up 7 to 14 days after surgery.
The proportion of patients achieving hemostatic success was calculated by treatment group. A 2-sided 95% confidence interval (CI) for the odds ratio of proportions of success was constructed using the method described by Koopman. If the lower limit of the 95% CI was greater than 0.80, then non-inferiority would be claimed. In the case that the lower limit of the 95% CI was not only greater than 0.80 but also greater than 1.0, this was considered evidence of superiority in terms of statistical significance at the 5% level (P<0.05). In this case, the P value associated with the test of superiority was calculated.

**Figure 8.** Percentages of patients in each treatment group that achieved hemostasis at 4, 7, and 10 minutes after randomization. At each time point, a significantly higher percentage of patients who received EVICEL® Fibrin Sealant (Human) versus absorbable hemostat achieved hemostasis. A significantly higher percentage of patients who received EVICEL® versus absorbable hemostat achieved hemostasis within 10 minutes (95.5% vs 81.2%; odds ratio = 1.18; 95% CI for the ratio, 1.04-1.36; P=0.0102; Figure 8). Significantly higher percentages of patients who received EVICEL® versus absorbable hemostat achieved hemostasis within 4 minutes (75.8% vs 53.6%; odds ratio = 1.41; 95% CI for the ratio, 1.10-1.86; P=0.0072) and 7 minutes (90.9% vs 76.8%; odds ratio = 1.18; 95% CI for the ratio, 1.02-1.40; P=0.0266). Success rates in the pediatric subgroup were consistent with those in the overall population (eg, hemostasis at 10 minutes: 100.0% vs 71.4%, respectively for EVICEL® and absorbable hemostat).
Results of additional effectiveness endpoints are provided in Table 7. The incidence of treatment failure was significantly ($P<0.05$) lower in the EVICEL® treatment group than in the absorbable hemostat treatment group (4.5% vs 18.8%, respectively). No patients who received EVICEL® experienced brisk bleeding requiring additional hemostatic measures during the 10-minute observation period compared with 5.8% of patients in the absorbable hemostat group (odds ratio = 1.06; 95% CI for the ratio, 1.00-1.16; $P=0.05$). The incidence of complications that were potentially related to bleeding was similar between the treatment groups (EVICEL®, 10.6%; absorbable hemostat, 15.9%; odds ratio = 0.67; 95% CI for the ratio, 0.28-1.56). Anemia and low hemoglobin levels were the most frequently reported complications that were considered to be potentially related to bleeding. The median TTH was significantly ($P<0.001$) shorter in the EVICEL® group versus the absorbable hemostat group (2.5 minutes vs 4.0 minutes, respectively).

A total of 68.7% of patients who received EVICEL® experienced at least 1 adverse event compared with 70.6% of patients who received absorbable hemostat. The most common adverse events (≥10% incidence in either treatment group) for patients who received EVICEL® versus absorbable hemostat were nausea (13.4% vs 8.8%, respectively), hypokalemia (11.9% vs 10.3%, respectively), insomnia (11.9% vs 8.8%, respectively), hypotension (7.5% vs 13.2%, respectively), and pyrexia (10.4% vs 8.8%, respectively). These adverse events were consistent with those expected for patients undergoing retroperitoneal or intra-abdominal surgical procedures, and no adverse event was judged to be related to either study treatment.

For patients who received EVICEL®, 17.9% of those patients experienced a serious adverse event compared with 22.1% of patients who received the absorbable hemostat. Three of the serious adverse events were considered possibly related to treatment, including 2 instances of abdominal abscess (1 for a patient who received EVICEL® and 1 for a patient in the absorbable hemostat treatment group) and 1 instance of pelvic abscess (absorbable hemostat treatment group). In the pediatric subpopulation, 1 patient (25.0%) who received EVICEL® experienced at least 1 adverse event; 6 patients (85.7%) who received absorbable hemostat experienced at least 1 adverse event.

### Table 7. Hemostatic Effectiveness of EVICEL® During Retroperitoneal or Intra-abdominal Surgery—Additional Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>EVICEL® (n = 66)</th>
<th>Absorbable hemostat (n = 69)</th>
<th>Odds ratio (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure, %</td>
<td>4.5</td>
<td>18.8</td>
<td>NA</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Complications potentially related to bleeding, %</td>
<td>10.6</td>
<td>15.9</td>
<td>0.67 (0.28-1.56)</td>
<td>NA</td>
</tr>
<tr>
<td>Median time to hemostasis, min</td>
<td>2.5</td>
<td>4.0</td>
<td>NA</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; NA, not applicable.
CONCLUSION

Results of this study demonstrate that EVICEL® Fibrin Sealant (Human) is safe and effective for achieving hemostasis for mild-to-moderate bleeding in soft tissue during non-emergent retroperitoneal or intra-abdominal surgery.
Summary of Preclinical Findings
Summary of Preclinical Findings

Preclinical studies conducted with EVICEL® focused on comparing it with CROSSEAL* Fibrin Sealant (Human) and other marketed fibrin sealants (Tissucol™ and Tisseel™) to assess its relative hemostatic efficacy, coverage area, viscosity and the stability of the clot once formed. These studies showed that the hemostatic properties of EVICEL® were comparable to those of CROSSEAL Fibrin Sealant in terms of time to hemostasis, clot stability, volume of product needed, and shelf life.51 These preclinical studies were conducted as part of an FDA registration process for gaining approval for EVICEL®.

To evaluate the stability of EVICEL® clot, a study was conducted in a rat model. In this study, the kinetics of clot disappearance over time was evaluated. This study revealed that the EVICEL® clot had a longevity comparable to that of CROSSEAL Fibrin Sealant and other marketed fibrin sealants (Tissucol™ and Tisseel™), indicating that the removal of endogenous plasminogen from EVICEL® compensates for the lack of the fibrinolysis inhibitor present in the other fibrin sealants. These results support the use of EVICEL® as an adjunct to hemostasis in surgical procedures.53

Since previous pharmacology studies showed no evidence of local intolerance or systemic toxicity, and because EVICEL® is formulated without tranexamic acid, toxicology studies were conducted on EVICEL® to evaluate the neurotoxicity of this fibrin sealant following intracerebral application in a rabbit model. Results showed that EVICEL® did not cause any treatment related local or systemic neurotoxicity.54

STUDY I: EVALUATION OF THE SAFETY AND EFFICACY IN HEPATIC WOUNDS IN RABBIT MODEL

Objective
To evaluate the local tolerance, systemic toxicity, and hemostatic properties of EVICEL® in comparison with CROSSEAL Fibrin Sealant following a single application on hepatic wounds in the rabbit.50

Description
Three groups, each containing 10 rabbits, were treated with EVICEL® with BAC2 (Human Fibrinogen Solution) from 2 different lots, and CROSSEAL Fibrin Sealant. Following a partial hepatectomy in each rabbit, the bleeding section was sprayed with at least 1 mL of the test product. Time to achieve hemostasis was recorded in each case. The animals were sutured, sacrificed after 14 ± 1 days, and subjected to macroscopic and microscopic examination of the treated site. Individual hematological analyses were performed.50
Results
The results are summarized in Table 8 below. The time to hemostasis and the mean volume of fibrin sealant used were similar in all groups.

Table 8. Rabbit Liver Study Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CROSSEAL* Fibrin Sealant</th>
<th>EVICEL® (BAC2 [Human Fibrinogen Solution]: Lot 1)</th>
<th>EVICEL® (BAC2 [Human Fibrinogen Solution]: Lot 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to hemostasis (sec)</td>
<td>&lt;49</td>
<td>&lt;51</td>
<td>&lt;52</td>
</tr>
<tr>
<td>Mean amount of FS used (mL)</td>
<td>1.2 ± 0.2</td>
<td>1.2 ± 0.4</td>
<td>1.4 ± 0.3</td>
</tr>
</tbody>
</table>

The incidence of adhesions was similar between the three groups.

Conclusions
Hemostatic properties of EVICEL® Fibrin Sealant (Human) were comparable to those of CROSSEAL Fibrin Sealant, and there was no evidence of local intolerance or systemic toxicity with EVICEL®. These results support the use of EVICEL® as an adjunct to hemostasis in surgical procedures.  

STUDY II: EVALUATION OF THE LONGEVITY OF EVICEL® IN ABDOMINAL WALL WOUNDS IN A RAT MODEL

Objective
BAC2 (Human Fibrinogen Solution) undergoes a processing step to remove plasminogen. As a result, it is not necessary to add the anti-fibrinolytic agent tranexamic acid (TA) to stabilize the product in vivo. The objective of this study was to compare the longevity (clot stability) of EVICEL® with CROSSEAL Fibrin Sealant, Tissucol™, and Tisseel™. This comparison was performed following a single application onto abdominal wall wounds in the rat.

Description
In 4 groups of 10 male animals each, a standardized abdominal wall defect (2x1 cm flap) that penetrates the abdominal wall muscles was sprayed with 1 mL of the test product (EVICEL®) or 1 of 3 reference fibrin sealants (CROSSEAL Fibrin Sealant, Tissucol™ or Tisseel™). Two animals from each of the 4 groups were sacrificed after 1, 3, 5, 7, and 10 ± 2 days (2 animals per time point). The remaining clot was extracted, weighed, and dissolved in a clot solubilizing solution (0.2 M NaOH and 7 M Urea) for clottable protein determination.

† Tissucol™, (Baxter Deutschland GmbH, EU registration No.6208244DB16). Fibrinogen component consists of: Protein: 80-120 mg/ml, Fibrinogen: 70-110 mg/ml; Factor XIII: 10-50 IU/ml; Fibronectin: 2-9 IU/ml; Aprotonin bovine: 3000 KIU/ml.

Tisseel™ VH; (Baxter Health Care Co-operation, A-1220 Vienna Austria, BLA #25, US License Number 140). Fibrin Sealant lyophilized. Fibrinogen component consists of: Protein: 100-130 mg/ml, Fibrinogen: 75-115 mg/ml; Aprotonin bovine: 2250-3750 KIU/ml.
In the EVICEL® group the clot was reduced to 80% in 9 days. To confirm these results, a further group of 10 animals implanted with EVICEL® were sacrificed after 9 days. The remaining clot from each animal was weighed and assessed for clottable protein.\textsuperscript{52}

**Results**

The quantity of clot remaining at different time points is summarized in Table 9. The clot was not completely absorbed after 12 days in either of the animals in the EVICEL® group. In animals treated with CROSSEAL* Fibrin Sealant (Human) and Tisseel™, complete absorption of the clot was seen in 1 of 2 animals after 12 days. In animals treated with Tissucol™, no clot was observed in either animal after 12 days.\textsuperscript{52}

<table>
<thead>
<tr>
<th>Parameter and Time</th>
<th>EVICEL®</th>
<th>CROSSEAL Fibrin Sealant</th>
<th>Tisseel™</th>
<th>Tissucol™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clot weight (g) at:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>0.33</td>
<td>0.35</td>
<td>0.29</td>
<td>0.33</td>
</tr>
<tr>
<td>3 days</td>
<td>0.21</td>
<td>0.19</td>
<td>0.24</td>
<td>0.18</td>
</tr>
<tr>
<td>5 days</td>
<td>0.07</td>
<td>0.05</td>
<td>0.24</td>
<td>0.12</td>
</tr>
<tr>
<td>7 days</td>
<td>0.12</td>
<td>0.11</td>
<td>0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>12 days</td>
<td>0.03</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Clottable protein (mg) at:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>20.5</td>
<td>23.4</td>
<td>25.6</td>
<td>31.7</td>
</tr>
<tr>
<td>3 days</td>
<td>13.9</td>
<td>15.3</td>
<td>23.9</td>
<td>16.3</td>
</tr>
<tr>
<td>5 days</td>
<td>6.2</td>
<td>5.5</td>
<td>22.8</td>
<td>13.8</td>
</tr>
<tr>
<td>7 days</td>
<td>8.8</td>
<td>8.3</td>
<td>13.6</td>
<td>4.1</td>
</tr>
<tr>
<td>12 days</td>
<td>2.9</td>
<td>0.7</td>
<td>2.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

The second group of animals treated with EVICEL® (n=10), which were euthanized after day 9, showed an average clot weight of 0.063 g (SD 0.035), and an average clottable protein of 5.2 mg (SD 2.6), equivalent to 19% and 25% of the respective average values at day 1. These results were consistent with those observed in the comparative study.

There was no statistically significant difference in the longevity of the clots formed from the different fibrin sealants. The results are depicted in Figures 9 and 10 below.\textsuperscript{52}
Conclusions

Longevity of the EVICEL® Fibrin Sealant (Human) clot in vivo is comparable to that of CROSSEAL Fibrin Sealant, and other marketed fibrin sealants such as Tissucol™ and Tisseel™. These results indicate that the removal of endogenous plasminogen from EVICEL® compensates for the lack of fibrinolysis inhibitor present in the other fibrin sealants.52

Note: Not intended to convey comparative safety or efficacy. Clot longevity comparison based on animal testing—the clinical significance of which has not been established.
STUDY III: NEUROTOXICITY EVALUATION OF A PLASMA-DERIVED FIBRIN SEALANT FOLLOWING SUBDURAL ADMINISTRATION IN THE RABBIT

Objective

Intracerebral application of CROSSEAL® Fibrin Sealant (Human) to rabbits at a dose equivalent to the human dose has shown to result in neurological symptoms. The cause of this neurotoxicity was determined to be tranexamic acid. Since EVICEL® is formulated without tranexamic acid, it was anticipated that neurotoxic effects would not be observed upon intracerebral application. The objective of this study was to evaluate the local tolerance and neurotoxicity of EVICEL® following subdural administration in the rabbit.

Description

The study was conducted with two batches of EVICEL®, with BAC2 (Human Fibrinogen Solution) from two different lots. A total dose of 0.5 mL of fibrin sealant was applied to two defects of the dura mater created on either side following bilateral parasagittal craniotomy. Sham operated animals were used as controls. Neurobehavioral observations were made; the animals were sacrificed after 14 ± 1 days; surgical sites were examined macroscopically and microscopically, and cerebrospinal fluid was analyzed.

Results

There were no abnormal clinical or neurobehavioral signs, no major macroscopic signs of local intolerance, and no treatment-related abnormal macroscopic findings in any of the test products.

Cerebrospinal fluid analysis did not reveal major signs of inflammation. There was no difference between the treatment with the test products and the sham procedure, beyond discrete inflammation observed in 2 animals treated with each of the test articles.

The microscopic tissue response to both EVICEL® batches was biologically significantly different from the tissue response within the sham-operated sites.

The two test articles were surrounded by fibrous tissue, infiltrated by heterophils and macrophages; merging with the dura mater. The inflammatory component of the response to the test articles decreased as it merged with the dura mater. Adhesions between the fibrous tissue and the pia mater generally involved the entire length of the defect and were more severe in animals receiving the test articles than were observed in the sham control animals.
Table 10. Cerebrospinal Fluid Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (Sham)</th>
<th>EVICEL® (BAC2 [Human Fibrinogen Solution]: Lot 1)</th>
<th>EVICEL® (BAC2 [Human Fibrinogen Solution]: Lot 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count (/mm³)</td>
<td>7 ± 10</td>
<td>15 ± 13</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>Red cell count (/mm³)</td>
<td>17,344 ± 38,962</td>
<td>23,756 ± 39,141</td>
<td>23,621 ± 24,010</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>0.30 ± 0.22</td>
<td>0.42 ± 0.30</td>
<td>0.46 ± 0.38</td>
</tr>
<tr>
<td>Fine cytology interpretation</td>
<td>No inflammation in 8/8 animals†</td>
<td>Discrete inflammation in 2/10 animals†</td>
<td>Discrete inflammation in 2/8 animals†</td>
</tr>
</tbody>
</table>

†Two animals from each group could not be assessed due to sampling problems.

Conclusions

No treatment related local or systemic signs of neurotoxicity were identified during the course of this study. Signs of local inflammatory reaction were more biologically significant in the two test article groups than in the sham control animals, and were associated with physiological processes of product degradation in the implanted tissues.  

OVERALL CONCLUSIONS

The preclinical studies described above demonstrate the following:

1. The hemostatic efficacy of EVICEL® Fibrin Sealant (Human) is comparable to that of CROSSEAL® Fibrin Sealant.  
2. There is no evidence of local intolerance or systemic toxicity with EVICEL® in vitro.  
3. Clot longevity of EVICEL® is comparable to that of other fibrin sealants which include antifibrinolytic agents in vivo.  
4. Intracerebral application of EVICEL® is not associated with any evidence of neurotoxicity.  

The findings of these pharmacological and toxicological studies support the safe use of EVICEL®.
Warnings and Precautions

Adverse Reactions and Drug Interactions
Warnings and Precautions

APPLICATION PRECAUTIONS

Apply EVICEL® as a thin layer. Excessive clot thickness may negatively interfere with the product’s efficacy and the wound healing process.

Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer EVICEL®. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.

When applying EVICEL® using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 20-25 psi. Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying EVICEL®, changes in blood pressure, pulse, oxygen saturation and end tidal CO2 should be monitored because of the possibility of occurrence of air or gas embolism.

INFECTION RISK FROM HUMAN PLASMA

Because EVICEL® is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to ETHICON Customer Support Center at (877) 384-4266. The physician should discuss the risks and benefits of this product with the patient.

Adverse Reactions

CLINICAL TRIALS EXPERIENCE

The most serious adverse events reported during clinical trials are abdominal abscess, ileus paralytic, urinary retention, staphylococcal and infection bacteria, graft infection, occluded graft, hematoma, bleeding abdominal incision.

The most common adverse events reported (≥5%) during clinical trials are bradychardia, nausea, hypokalemia, insomnia, hypotension, pyrexia, graft infection, vascular graft occlusion, oedema peripheral, constipation.

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 practice.
a) Retroperitoneal and Intra-Abdominal Surgery
In a controlled study in retroperitoneal and intra-abdominal surgery involving 135 patients, 46 of 67 patients (69%) treated with EVICEL® and 48 of 68 control group patients (71%) experienced one or more adverse events during the study. No event was reported at least 5% more frequently in the EVICEL® group than in the control group.

b) Vascular Surgery
In controlled studies in vascular surgery involving 167 patients (147 patients in a Phase III study and 20 additional patients in a Phase II study), no adverse event in the fibrin sealant group (75 and 10 patients in the Phase III and II studies respectively) with frequency >5% occurred significantly more often than in the control group (72 and 10 patients in the Phase III and II studies respectively).

c) Liver Surgery
In controlled studies in liver surgery involving 154 patients, 68 adverse events were reported for at least 5%, of which only bradycardia had a higher frequency (p=0.041) in the fibrin sealant group (9.5%) than in the control group (2.5%).

POST MARKETING EXPERIENCE
A post marketing fatality was reported in association with the use of EVICEL® when applied using a spray device. The case involved an attempt to stop active bleeding by applying EVICEL® using a spray device attached to a wall unit at a higher than recommended pressure for the spray device. In addition, the spray head was placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant. The patient suffered a fatal air embolism.

The following adverse reactions reflect what has been reported in post marketing experience with EVICEL®:

- **Immune system disorders**: anaphylactic responses, hypersensitivity
- **Cardiovascular disorders**: bradycardia, tachycardia, cardiac arrest, hypertension
- **Respiratory, thoracic and mediastinal disorders**: dyspnea, tachypnea, hyperventilation
- **Skin and subcutaneous tissue disorders**: urticaria
- **General disorders and administration site conditions**: edema, pyrexia
- **Injury, poisoning and procedural complication**: seroma

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

**Drug Interactions**
No drug interactions are known.
Precautions
Precautions

GENERAL
The BAC2 (Human Fibrinogen Solution) and thrombin components of EVICEL® must only be administered topically.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY
Long-term animal studies have not been performed to evaluate the carcinogenic potential of EVICEL® owing to the human origin of both the fibrinogen and the thrombin contents. The effect of EVICEL® on fertility has not been evaluated.

Results of studies performed on bacteria to determine mutagenicity were negative for BAC (containing fibrinogen, citrate, glycine, tranexamic acid, and arginine hydrochloride), thrombin alone, tri-n-butyl phosphate alone, and Triton X-100 alone at all concentrations tested. All concentrations of the combination of tri-n-butyl phosphate and Triton X-100 also tested negative in assays performed to determine mammalian cell mutagenicity, chromosomal aberrations, and micronuclei induction.

PREGNANCY CATEGORY C
Adequate and well-controlled studies in pregnant women have not been performed. EVICEL® should be used in pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus. Studies to evaluate the potential reproductive/developmental toxicity of EVICEL® have not been performed owing to the human origin of both the fibrinogen and the thrombin contents. Intravenous injection of the combination of tri-n-butyl phosphate and Triton X-100 into pregnant rats at doses up to approximately 600-fold (tri-n-butyl phosphate, 900 µg/kg/day) and 3000-fold (Triton X-100, 4500 µg/kg/day) the human dose, resulted in increased post-implantation loss and an increased number of late resorptions. No embryo-fetal adverse effects were observed at doses up to 200-fold (tri-n-butyl phosphate, 300 µg/kg/day) and 1000-fold (Triton X-100, 1500 µg/kg/day) the human dose. Pregnant rabbits injected intravenously with the combination of tri-n-butyl phosphate and Triton X-100 at doses approximately 300-fold (tri-n-butyl phosphate, 450 µg/kg/day) and 1500-fold (Triton X-100, 2250 µg/kg/day) the human dose had increased resorption rates, decreased fetal body weights, and an increased number of runts. No embryo-fetal adverse effects were observed at doses up to 100-fold (tri-n-butyl phosphate, 150 µg/kg/day) and 500-fold (Triton X-100, 750 µg/kg/day) the human dose.
**PEDIATRIC USE**

Limited data are available to support the safety and effectiveness of EVICEL® in children. No data is currently available for ages 0 to 6 months.

Of 135 patients undergoing retroperitoneal and intra-abdominal surgery who were included in the adequate and well-controlled study of EVICEL®, 4 patients treated with EVICEL® were aged 16 years or younger. Of these, 2 were children aged 2 to 11 years and 2 were adolescents of 12 to 16 years.

Pediatric patients for vascular surgery are rare and were therefore not included in the clinical trials involving vascular surgery.

Of the 155 patients undergoing liver surgery who were treated in adequate and well-controlled studies, eight were pediatric patients. Of these, five were less than 2 years old and three were between 2 and 12 years old.

Use of EVICEL® in pediatric patients above age 6 months is supported by these data and by extrapolation of findings for safety and efficacy in adults. Data can not be extrapolated to ages 0 to 6 months.

**GERIATRIC USE**

Clinical trials included 101 patients of 65 years of age or older (30 undergoing retroperitoneal or intra-abdominal surgery, 24 undergoing liver surgery and 47 undergoing vascular surgery).

No overall differences in safety or effectiveness were observed between the elderly and younger patients.
Dosage and Administration
Dosage and Administration

FOR TOPICAL USE ONLY. DO NOT INJECT.

EVICEL® should be sprayed or dripped onto the tissue in short bursts (0.1 to 0.2 mL) to produce a thin, even layer. If the hemostatic effect is not complete, a second layer should be applied. The amount of EVICEL® required depends on the area of tissue to be treated and the method of application. As an approximate guide, if a layer of 1 mm thickness is produced by spraying EVICEL®, the surface areas that can be covered by each of the kit sizes are given in Table 11.

Table 11. Approximate Surface Area That Can Be Covered by a 1-mm Layer of Sprayed EVICEL®

<table>
<thead>
<tr>
<th>EVICEL® Package Size (Total Volume)</th>
<th>Area of Coverage With Layer of 1 mm Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mL (2.0 mL)</td>
<td>20 cm²</td>
</tr>
<tr>
<td>2.0 mL (4.0 mL)</td>
<td>40 cm²</td>
</tr>
<tr>
<td>5.0 mL (10.0 mL)</td>
<td>100 cm²</td>
</tr>
</tbody>
</table>

Standard surgical techniques for hemorrhage control, including suture ligature and cautery, should be used prior to the application of EVICEL®. Although a dry field is not essential, excess blood should be removed from the site of application if possible, and EVICEL® should then be applied with the application device supplied (Figure 11). This device allows for the simultaneous application of equal amounts of the two components and ensures mixing, which is essential to achieve optimal efficacy. EVICEL® forms a transparent layer on application through which specific bleeding points may be observed, in which case these may be sutured or electrocauterized through the layer of EVICEL®.
Figure 11. Application Device

Figure 12. Optional 35 cm Rigid Tip

Figure 13. Optional 45 cm Flexible Tip
Instructions for use are presented below.

**THAWING OF BIOLOGICAL ACTIVE COMPONENT 2 AND THROMBIN**

• 2°C to 8°C (refrigerator); vials thaw within 1 day; or
• 20°C to 25°C (room temperature); vials thaw within 1 hour.
• 37°C; vials thaw within 10 minutes and must not be left at this temperature for longer than 10 minutes. The temperature must not exceed 37°C.

**PREPARATION OF EVICEL® AND APPLICATOR**

Note: Device assembly and product aspiration into the device MUST take place in a sterile operating room.

**Outside of Sterile Field Preparation**

1. Select package by size (1 mL, 2 mL, 5 mL).
2. Open the box containing the device and take out the inner packaging.

1. Remove the cover of the outer packaging without touching the contents.

1. Using sterile technique, empty the inner package onto the sterile field.

1. Ensure that the two vials of product (thrombin and BAC2 [Human Fibrinogen Solution]) have been thawed according to package insert instructions.
2. Flip off plastic caps of the two vials of product.
3. Do not touch sterile rubber stoppers.
Sterile Field Preparation

Remove the cover of the inner packaging and empty contents onto the sterile field.

1. Place each vial securely into the sterile vial cup held by a person who has scrubbed. Non-sterile field: Do not touch vial cups.

2. Loosen the syringe pistons of the device by sliding them back and forth. Holding the vials upright, the person who has scrubbed should press each vial connector firmly into the exposed portion of the rubber stopper on each vial.

3. Hold the syringe barrels with vials facing upward and slowly aspirate both products into the syringes. If necessary to expel air, product may be slowly injected back into vials and aspirated again.

4. Hold the syringe barrels with one hand, and gently turn the vial counter-clockwise with the other hand. The vial connector, vial and vial cup combination will disconnect automatically.

5. The device is now ready for drip use.

6. If spraying is required connect male luer-lock to the short air tube on the device in the sterile field. The long air tube with the 0.2 μm filter is then connected by inserting the female luer-lock onto the EVICEL® Fibrin Sealant (Human) pressure regulator.

7. Use the pressure regulator according to manufacturer’s instructions.

8. To spray, set pressure at 15 to 25 psi and hold device tip 10 to 15 cm (4 to 6 inches) from tissue surface during open procedures and a minimum of 4 cm during lap procedures.
Connecting 35 cm Rigid Tip or 45 cm Flexible Tip

Note: Assemble this device in the OR using proper sterile technique. Rigid Tip or Flexible Tip may be exchanged at any time during the surgical procedure.

1. Circulating Nurse: Open the pouch and empty the Rigid Tip or 45 cm Flexible Tip onto the sterile field.

2. Scrub Nurse: To remove the short tip, hold the syringe barrels and loosen luer connectors by turning nuts counter-clockwise. Discard short tip. To minimize risk of device clogging, the short tip should not be reattached.

3. Attach the 35 cm Rigid Tip or 45 cm Flexible Tip to the syringe body by rotating the luer connectors clockwise to tighten.

4. Ensure tip is firmly connected before use.

Note: The 35 cm Rigid Tip or 45 cm Flexible Tip can be used for drip or spray purposes. If the tip should become clogged during use, any visible clot at the end of the tip can be wiped off or removed using sterile gauze.
At 37°C, vials thaw within 10 minutes and must not be left at this temperature for longer than 10 minutes. The temperature must not exceed 37°C.

**METHOD OF APPLICATION BY DRIPPING**

Keeping the tip of the applicator as close to the tissue surface as possible—but without touching the tissue during application—apply individual drops onto the area to be treated. The drops should be allowed to separate from each other and from the tip of the applicator. If the applicator tip becomes blocked, it can be cut back in 0.5-cm increments.

**METHOD OF APPLICATION BY SPRAYING**

- Connect the female Luer-Lock end of the short air tube on the application device to the male Luer-Lock end of the long air tube supplied.
- Connect the female Luer-Lock end of the long air tube (with the 0.2-μm bacteriological filter) to an air regulator capable of delivering between 15 and 25 psi of pressure.
- The air regulator should be used in accordance with the manufacturer’s instructions.
- An air pressure of 15 to 25 psi (measured by airflow) should be used for spraying.
- The distance between the applicator tip (nozzle) and the tissue surface should ideally be between 10 and 15 cm spraying during open procedures and a minimum of 4 cm spraying during minimally invasive procedures.

For more information, please contact the ETHICON Customer Support Center at 1-877-ETHICON (877-384-4266).
How Supplied
How Supplied

EVICEL® is supplied as a kit consisting of two separate packages:

- One package containing 1 vial each of BAC2 (Human Fibrinogen Solution) (55-85 mg/mL fibrinogen) and thrombin (800-1200 IU/mL human thrombin and 5.6-6.2 mg/mL calcium chloride) solutions (in equivalent 1 mL, 2 mL, or 5 mL volumes, initially frozen).

- Another package (application device package) containing the application device, sterile vial cups, and long air tube with 0.2 μm bacteriological filter.

<table>
<thead>
<tr>
<th>ORDER CODE</th>
<th>DESCRIPTION (Total Volume)</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3901</td>
<td>1 mL kit (2 mL)</td>
<td>63713-390-11</td>
</tr>
<tr>
<td>3902</td>
<td>2 mL kit (4 mL)</td>
<td>63713-390-22</td>
</tr>
<tr>
<td>3905</td>
<td>5 mL kit (10 mL)</td>
<td>63713-390-55</td>
</tr>
<tr>
<td>3908</td>
<td>35 cm Rigid Tip – Set of 3</td>
<td>N/A</td>
</tr>
<tr>
<td>3909</td>
<td>45 cm Flexible Tip – Set of 3</td>
<td>N/A</td>
</tr>
<tr>
<td>1938</td>
<td>Pressure Regulator for spray delivery</td>
<td>N/A</td>
</tr>
</tbody>
</table>

When frozen, BAC2 (Human Fibrinogen Solution) and thrombin appear as white to slightly yellowish opaque masses. When thawed, the solutions are clear to slightly opalescent and colorless to slightly yellowish, respectively. The application device and long air tube are sterile and for single use only.
Special Handling and Storage Conditions
Special Handling and Storage Conditions

For long-term storage, store frozen vials at -18°C or colder for up to 2 years. Unopened vials can be stored after thawing at 2°C to 8°C under refrigeration for up to 30 days. The application device package should be stored separately at room temperature.

• Do not use after the expiration date stated on the box, after 30 days if stored at 2°C to 8°C after thawing, or after 24 hours at room temperature.

• Do not refreeze thawed BAC2 (Human Fibrinogen Solution) or thrombin vials.

• Do not refrigerate EVICEL® once at room temperature. Discard unused product after 24 hours at room temperature.

• Do not mix BAC2 (Human Fibrinogen Solution) or thrombin with any other product.

• Discard if the packaging of any of the components of EVICEL® is damaged.
References


48. EVICEL® Fibrin Sealant (Human) Full Prescribing Information, Ethicon, Inc.


50. Data on File, Ethicon, Inc., Evaluation of the safety and haemostatic properties of a plasma derived fibrin sealant following application to hepatic wounds in the rabbit.


52. Data on File, Ethicon, Inc., A prospective, randomized, controlled evaluation of Fibrin Sealant 2 (FS2) as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal or intra-abdominal surgery.


54. Data on File, Ethicon, Inc., Neurotoxicity evaluation of plasma derived fibrin sealant following subdural administration in the rabbit.


EVICEL® Fibrin Sealant (Human) is indicated as an adjunct to hemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

**Important Safety Information**

- For topical use only. Do not inject directly into the circulatory system.
- Not indicated 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.
- Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants. These events appear to be related to the use of the spray device at higher than recommended pressures and in close proximity to the surface of the tissue. Follow labeled application instructions regarding pressure range and distance when using a spray device and monitor patients for the possibility of air or gas embolism.
- 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.
- Anaphylactic reactions may occur.
- Most common adverse events reported in clinical trials (≥5%) are bradycardia, nausea, hypokalemia, insomnia, hypotension, pyrexia, graft infection, vascular graft occlusion, oedema peripheral, constipation.

*Please see the Full Prescribing Information enclosed.*