

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**EVICEL Fibrin Sealant (Human),**

**For Topical Use Only**

Frozen solutions of BAC2 (fibrinogen) and Thrombin

**Initial U.S. approval: 2003**

**-----RECENT MAJOR CHANGES-----**

WARNINGS and PRECAUTIONS; Application Precautions (5.1) 09/2009

**-----INDICATIONS AND USAGE-----**

- EVICEL is a fibrin sealant 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 (1).

**-----DOSAGE AND ADMINISTRATION-----**

- **For Topical Use Only. Do not inject directly into the circulatory system.** (2, 4)
- After thawing, use the two components of EVICEL (BAC2 and Thrombin) within 24 hours if stored at room temperature, or within 30 days if stored refrigerated (2.1,16).
- Spray or drip EVICEL Fibrin Sealant (Human) onto the tissue in short bursts (0.1-0.2 ml) to produce a thin, even layer. If the hemostatic effect is not complete, apply a second layer. The amount of EVICEL required depends upon the area of tissue to be treated and the method of application (2.2).
- Vials are for single use only. Discard unused contents (2.2, 16).

**-----DOSAGE FORMS AND STRENGTHS-----**

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

- A package containing one vial each of BAC2 (55-85 mg/ml fibrinogen) and Thrombin (800-1200 IU/ml human thrombin) frozen solutions.
- A spray application device.

The different EVICEL dosage forms include the following sizes:

BAC2 Vial Size	Thrombin Vial Size	Package Size
1.0 ml	1.0 ml	2.0 ml

2.0 ml	2.0 ml	4.0 ml
5.0 ml	5.0 ml	10.0 ml

-----CONTRAINDICATIONS-----

- Do not inject directly into the circulatory system (4.1)
- Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products. (4.2)
- Do not use for the treatment of severe or brisk arterial bleeding.(4.3)

-----WARNINGS AND PRECAUTIONS-----

- 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 in close proximity to the surface of the tissue (5.1).
- May carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite manufacturing steps designed to reduce the risk of viral transmission (5.2).

-----ADVERSE REACTIONS-----

Most common adverse events reported in clinical trials ( $\geq 5\%$ ) are bradycardia, nausea, hypokalemia, insomnia, hypotension, pyrexia, graft infection, vascular graft occlusion, oedema peripheral, constipation (6.1).

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

-----DRUG INTERACTIONS-----

No drug interactions are known.

**See 17 for PATIENT COUNSELING INFORMATION**

Revised: 11/2009

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

## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

EVICEL<sup>®</sup> 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.

### **2 DOSAGE AND ADMINISTRATION**

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

#### **2.1 Thawing**

Thaw the two components of EVICEL<sup>®</sup> (BAC2 and Thrombin) in one of the following ways:

- 2°C to 8°C (refrigerator); vials thaw within 1 day; or
- 20°C to 25°C (room temperature); vials thaw within 1 hour; or
- 37°C; 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.

#### **2.2 Preparation Prior to Application**

Once thawed, use the components of EVICEL<sup>®</sup> (BAC2 and Thrombin), within 30 days if refrigerated and/or within 24 hours, if stored at room temperature.

Do not use after the expiration date stated on the box, or after 30 days if refrigerated after thawing. Do not re-freeze EVICEL<sup>®</sup> once it has been thawed. Do not refrigerate EVICEL<sup>®</sup> after storage at room temperature. Discard unused product after 24 hours at room temperature.

Discard if the packaging of EVICEL<sup>®</sup> is damaged.

While maintaining a sterile surgical field, prepare the product assembly as follows:

- a) Draw the BAC2 and Thrombin into the application device (see diagram enclosed in the application device package).
- b) Both syringes of the application device should be filled with equal volumes and should not contain air bubbles.
- c) Carefully remove the vial assembly. Use a gentle rotation to ensure valve engagement.

#### **2.3 Application Techniques**

For Topical Use Only. Apply EVICEL<sup>®</sup> to the surface of bleeding tissue only. Do not inject directly into the circulatory system.

Spray or drip EVICEL<sup>®</sup> in short bursts (0.1-0.2 ml) onto the tissue to produce a thin, even layer. If the hemostatic effect is not complete, apply a second layer. The amount of EVICEL<sup>®</sup> required depends upon 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<sup>®</sup>, the surface areas that can be covered by each of the kit sizes are given in table 1.

**Table 1: Area of coverage of each kit size**

BAC2 Vial Size	Thrombin Vial Size	Package Size	Area of Coverage with Layer of 1 mm Thickness
1.0 ml	1.0 ml	2.0 ml	20 cm <sup>2</sup>
2.0 ml	2.0 ml	4.0 ml	40 cm <sup>2</sup>
5.0 ml	5.0 ml	10.0 ml	100 cm <sup>2</sup>

Use standard surgical techniques for hemorrhagic control, including suture, ligature and cautery, prior to the application of EVICEL<sup>®</sup>. Remove excess blood from the site of application if possible, although a dry field is not essential. Apply EVICEL<sup>®</sup> with the application device supplied. EVICEL<sup>®</sup> forms a transparent layer on application through which specific bleeding points may be observed; these bleeding points may be sutured or electrocauterized through the layer of EVICEL<sup>®</sup>.

Vials are for single use only. Discard unused contents (see *HOW SUPPLIED/STORAGE and HANDLING (16)*).

#### Application by Dripping

- a) Keep the tip of the applicator as close to the tissue surface as possible, but without touching the tissue during application.
- b) Apply individual drops to the surface area to be treated.
- c) Allow the drops to separate from each other and from the tip of the applicator. If the applicator tip becomes blocked, wipe the yellow catheter tip clean or cut it back in 0.5 cm increments.

#### Application by Spraying

- a) Connect the short air tube on the application device to the luer-lock end of the long air tube.
- b) Connect the luer-lock of the air tube (with the 0.2 µm filter) to a pressure regulator capable of delivering between 15-25 psi of pressure.
- c) Utilize spray pressure that is within the recommended guidelines by the device manufacturer [e.g., an air pressure of 15-25 psi (measured by airflow)] (see *WARNINGS and PRECAUTIONS, Application Precautions (5.1) and ADVERSE REACTIONS, Post Marketing (6.2)*).
- d) Utilize air or gas pressure that is within the recommended guidelines by the device manufacturer during laparoscopic or thoracoscopic procedures.

- e) Carefully monitor insufflation pressure in all such procedures.
- f) Ensure that distance between the spray head and the application bed is within the recommended guidelines by the device manufacturer. The distance between the nozzle and the tissue surface should ideally be between 10 and 15 cm when spraying in open surgery, and at least 4 cm when spraying in laparoscopic or thoracoscopic procedures (see *WARNINGS and PRECAUTIONS, Application Precautions (5.1) and ADVERSE REACTIONS, Post Marketing (6.2)*).

See instructions enclosed in the application device package.

### 3 DOSAGE FORMS AND STRENGTHS

EVICEL<sup>®</sup> is supplied as a kit consisting of two separate packages:

- A package containing one vial each of BAC2 (55-85 mg/ml fibrinogen) and Thrombin (800-1200 IU/ml human thrombin) frozen solutions.
- A spray application device.

The different EVICEL<sup>®</sup> dosage forms include the following sizes (Table 2):

**Table 2: EVICEL<sup>®</sup> package sizes**

BAC2 Vial Size	Thrombin Vial Size	Package Size
1.0 ml	1.0 ml	2.0 ml
2.0 ml	2.0 ml	4.0 ml
5.0 ml	5.0 ml	10.0 ml

### 4 CONTRAINDICATIONS

#### 4.1 Intravascular Application

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

#### 4.2 Hypersensitivity

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

#### 4.3 Arterial Bleeding

Do not use EVICEL<sup>®</sup> for treatment of severe or brisk arterial bleeding. In these situations, EVICEL<sup>®</sup> will be washed away in the flow of blood before hemostasis can be attained.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Application Precautions**

Apply EVICEL<sup>®</sup> 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<sup>®</sup>. This event appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

When applying EVICEL<sup>®</sup> 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<sup>®</sup>, changes in blood pressure, pulse, oxygen saturation and end tidal CO<sub>2</sub> should be monitored because of the possibility of occurrence of air or gas embolism.

### **5.2 Infection Risk from Human Plasma**

Because EVICEL<sup>®</sup> 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.

## **6 ADVERSE REACTIONS**

### **6.1 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 ( $\geq 5\%$ ) 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<sup>®</sup> 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 EVICE<sup>®</sup>L 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%).

## 6.2 Post Marketing Experience

A post marketing fatality was reported in association with the use of EVICEL<sup>®</sup> when applied using a spray device. The case involved an attempt to stop active bleeding by applying EVICEL<sup>®</sup> 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<sup>®</sup>:

**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.

## **7 DRUG INTERACTIONS**

No drug interactions are known.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C

Animal reproduction studies have not been conducted with EVICEL<sup>®</sup>. It is not known whether EVICEL<sup>®</sup> can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EVICEL<sup>®</sup> should be given to a pregnant woman only if clearly needed.

### **8.2 Labor and Delivery**

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

### **8.3 Nursing Mothers**

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

### **8.4 Pediatric Use**

Limited data are available to support the safety and effectiveness of EVICEL<sup>®</sup> in children. No data are 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<sup>®</sup>, 4 patients treated with EVICEL<sup>®</sup> 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<sup>®</sup> 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.

## 8.5 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 differences in safety or effectiveness were observed between the elderly and younger patients.

## 11 DESCRIPTION

EVICEL<sup>®</sup> is manufactured from pooled human plasma. EVICEL<sup>®</sup> is provided as a single use kit consisting of two packages: One package contains one vial of Biological Active Component 2 (BAC2) and one vial of Thrombin. The second package contains a sterile spray application device. The two components (BAC2 and Thrombin) should be mixed and applied topically as described in the Dosage and Administration Section (2).

The BAC2 and Thrombin components 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**

BAC2 is a sterile solution, pH 6.7-7.2, which consists mainly of a concentrate of human fibrinogen. Fibrinogen is a protein from human blood that forms a clot when combined with thrombin.

The composition of the BAC2 solution is as follows:

#### **Active ingredient:**

Concentrate of human fibrinogen (55-85 mg/ml)

#### **Other Ingredients:**

Arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, water for injection (WFI)

### **Thrombin**

Thrombin is a sterile solution, pH 6.8-7.2, which contains purified human thrombin that activates clotting of the final combined product. Thrombin is a specific protease that transforms the fibrinogen contained in BAC2 into fibrin.

The composition of the Thrombin solution is as follows:

#### **Active Ingredient:**

Human thrombin (800-1200 IU/ml)

#### **Other Ingredients:**

Calcium chloride, human albumin, mannitol, sodium acetate, water for injection (WFI)

Cryoprecipitate, which is the starting material for BAC2, and cryo-poor plasma, which is the starting material for the production of Thrombin are both made from pooled human plasma that is obtained from US licensed plasma collection centers. BAC2 is manufactured from pooled Human Source plasma and Thrombin is manufactured from pooled Human Source or Recovered plasma. All the plasma is obtained from US licensed plasma collection centers. Cryoprecipitate manufacture may be performed by Talecris Biotherapeutics, Inc., 155 Duryea Road, Melville, NY 11747 (License No. 1716).

### **Viral Clearance**

Individual plasma units which are obtained for the production of EVICEL<sup>®</sup> are tested by FDA-licensed serological tests for HBsAg, HIV 1 & 2 Ab and HCV Ab as well as FDA-licensed Nucleic Acid Testing (NAT) methods for HCV and HIV-1. Recovered plasma units are also tested for HTLV I/II.

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. The plasma units are tested by NAT for HAV, HBV. All tests for HIV, HCV, HBV and HAV must be negative (non-reactive). However, since the effectiveness of these test methods in detecting low levels of viral material is still under investigation, the significance of a negative result for these viruses is unknown. NAT for parvovirus B19 is also performed, and the level of contamination is not permitted to exceed 10,000 copies/ml. This limit is applied to restrict the viral load of parvovirus B19 in the starting plasma pool.

In addition to the screening of plasma, each manufacturing pool is tested for HBsAg, HIV-1 & 2 Ab, HCV by NAT and Parvovirus B19 by NAT. Manufacturing pool testing, however, has a lower sensitivity than that of individual unit testing.

The manufacturing procedure for EVICEL<sup>®</sup> includes processing steps which are designed to reduce the risk of viral transmission. In particular, both BAC2 and Thrombin undergo two discrete virus inactivation/removal steps, summarized in table 3.

**Table 3: Steps for the reduction of viral transmission risk**

Step	Component	
	BAC2	Thrombin
1	Solvent detergent treatment (1% TnBP, 1% Triton X-100) for 4 hours at 30°C	Solvent detergent treatment (1% TnBP, 1% Triton X-100) for 6 hours at 26°C
2	Pasteurization (10 hours at 60°C)	Nanofiltration

BAC2 is manufactured by treatment of cryoprecipitate with aluminum hydroxide gel to adsorb the Vitamin K dependent clotting factors and it is then incubated with a solvent detergent (SD) mixture (1% TnBP, 1% Triton X-100) for 4 hours at 30°C. The SD reagents

are removed by castor oil extraction and reverse phase chromatography (C-18 column) and the preparation is subsequently treated by pasteurization.

Prior to pasteurization, sucrose and glycine are added as stabilizers. The solution is heated to 60±0.5°C and maintained at that temperature for 10 hours. After pasteurization, the stabilizers used for heat treatment are removed by diafiltration and the product is concentrated by ultrafiltration. An affinity chromatography step is then used to remove plasminogen from the product, after which it is concentrated. After concentration the solution is formulated, sterile filtered and aseptically filled and frozen.

Thrombin is manufactured by chromatographic purification of prothrombin from cryo-poor plasma followed by activation with calcium chloride. The manufacturing process includes two separate steps for inactivation or removal of viruses. The first of these is treatment with a SD mixture (1% TnBP, 1% Triton X-100) for 6 hours at 26°C to inactivate lipid enveloped viruses.

The SD 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 efficacy of the virus inactivation/removal procedures in inactivating a range of viruses has been assessed using viruses with a range of physico-chemical characteristics. The results of virus removal/inactivation validation studies are summarized in table 4.

**Table 4: Results of virus removal/inactivation in validation studies**

**a) BAC2**

<b>Virus</b>	<b>HIV-1</b>	<b>BVDV</b>	<b>PRV</b>	<b>EMCV</b>	<b>HAV</b>	<b>CPV</b>
<b>Reduction factor (log<sub>10</sub>)</b>						
SD Treatment	>4.42	>4.39	>3.96	Not Done	Not Done	0.0
Pasteurization	>4.39	>5.46	Not Done	3.69	>5.78	1.33
Global Reduction Factor	<b>&gt;8.81</b>	<b>&gt;9.85</b>	<b>&gt;3.96</b>	<b>3.69</b>	<b>&gt;5.78</b>	<b>1.33</b>

**b) Thrombin**

<b>Virus</b>	<b>HIV-1</b>	<b>SBV</b>	<b>BVDV</b>	<b>PRV</b>	<b>EMCV</b>	<b>HAV</b>	<b>CPV</b>
<b>Reduction factor (log<sub>10</sub>)</b>							
SD Treatment	>5.82	>5.31	>4.74	>4.25	Not Done	Not Done	0.0
Nanofiltration	>4.36	>5.32	Not Done	>5.47	6.37	6.95	5.85
Global Reduction Factor	<b>&gt;10.18</b>	<b>&gt;10.63</b>	<b>&gt;4.74</b>	<b>&gt;9.72</b>	<b>6.37</b>	<b>6.95</b>	<b>5.85</b>

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 fibrin adhesion system initiates the last phase of physiological blood coagulation. Thrombin activates the conversion of fibrinogen into fibrin, which occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from Factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both the conversion of fibrinogen and the crosslinkage of fibrin.

### **12.2 Pharmacodynamics**

Pharmacokinetic studies were not conducted.

Clinical studies demonstrating haemostasis were conducted in a total of 167 patients undergoing vascular surgery and in a total of 135 patients undergoing retroperitoneal and intra-abdominal surgery. Efficacy data is provided in section 14.

### **12.3 Pharmacokinetics**

Because EVICEL<sup>®</sup> is for topical use only and intravascular administration is contraindicated (*see CONTRAINDICATIONS, Intravascular Application (4.1)*), pharmacokinetic studies were not performed.

Studies have been conducted in rabbits to evaluate the absorption and elimination of thrombin when applied to the cut surface of the liver resulting from partial hepatectomy. Using <sup>125</sup>I-thrombin it was shown that a slow absorption of biologically inactive peptides resulting from the breakdown of thrombin occurred, reaching a C<sub>max</sub> in the plasma after 6-8 hours. At the C<sub>max</sub>, the plasma concentration represented only 1-2% of the applied dose. The systemic exposure to thrombin when it is administered directly to a hepatic wound was estimated to be approximately equivalent to that generated by a minor hemorrhage.

Fibrin sealants are metabolised in the same way as endogenous fibrin, by fibrinolysis and phagocytosis. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Local Tolerance and Acute-Repeat Toxicology Studies**

EVICEL<sup>®</sup> has been classified as non-irritant in the Primary Cutaneous Irritation Test and slightly irritant in the Ocular Irritation test.

No toxicological effects due to the solvent detergent reagents (TnBP and Triton X-100) used in the virus inactivation procedure are expected based on acute and repeat toxicity studies and since the residual levels are less than 5µg/ml.

### **13.2 Neurotoxicity**

Neurotoxicity studies performed with EVICEL<sup>®</sup> confirmed that subdural administration in the rabbit was not associated with any evidence of neurotoxicity.

### **13.4 Carcinogenesis**

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

### **13.5 Mutagenesis**

Neither BAC2 nor Thrombin solution induces mutagenic effects in the Ames test. Studies performed in bacteria to determine mutagenicity were negative for Thrombin alone, BAC (containing fibrinogen, citrate, glycine, tranexamic acid, and arginine hydrochloride), TnBP alone, and Triton X-100 alone 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.

### **13.6 Fertility**

The effect of EVICEL<sup>®</sup> on fertility has not been evaluated.

Reproductive studies performed in rats with the combination of TnBP and Triton X-100 at doses up to approximately 600-fold (TnBP, 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 (TnBP, 300 µg/kg/day) and 1000-fold (Triton X-100, 1500 µg/kg/day) the human dose. Other studies performed with the combination of TnBP at doses approximately 300-fold (TnBP, 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 (TnBP, 150 µg/kg/day) and 500-fold (Triton X-100, 750 µg/kg/day) the human dose.

## **14 CLINICAL STUDIES**

### **a) Retroperitoneal and Intra-Abdominal Surgery**

In a prospective, randomized, controlled evaluation of the hemostatic efficacy of EVICEL<sup>®</sup> as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal or intra-abdominal surgery, EVICEL<sup>®</sup> was shown to be superior to the control product (Surgicel, oxidized regenerated cellulose) in achieving hemostasis in less than 10 minutes (see Table 5). Superiority was also established at the secondary efficacy endpoints of 7 and 4 minutes.

**Table 5: Efficacy results in retroperitoneal and intra-abdominal surgery**

Variable	EVICEL <sup>®</sup> n = 66	Control n = 69	Relative Risk (RR)	95% CI for RR
Hemostasis at 10 min	63 (95.5%)	56 (81.2%)	1.18	1.04; 1.36
Hemostasis ≤ 7 min	60 (90.9%)	53 (76.8%)	1.18	1.02; 1.40
Hemostasis ≤ 4 min	50 (75.8%)	37 (53.6%)	1.41	1.10; 1.86

b) Vascular Surgery

A prospective, randomized study was performed to compare the hemostatic efficacy of fibrin sealant versus manual compression during vascular surgical procedures utilizing polytetrafluoroethylene graft material on end-to-side femoral artery anastomosis or upper extremity vascular access arterial anastomosis.

A difference ( $p < 0.001$ ) in time to hemostasis was observed: 83.3% of the treatment subjects as compared to 39.7% of control subjects achieved hemostasis by 4 minutes (see Table 6).

**Table 6: Efficacy results in vascular surgery**

Number (%) of patients achieving hemostasis	EVICEL <sup>®</sup>	Manual Compression
	n=72	n=68
At 4 minutes	60 (83.3%)	27 (39.7%)
≤7 minutes	63 (87.5%)	42 (61.8%)
≤10 minutes	66 (91.7%)	48(70.6%)

c) Liver Surgery

EVICEL<sup>®</sup> was compared in a pivotal Phase III single-blind, randomized, parallel-group, multi-center study to FDA-approved control topical hemostatic agents in 121 patients undergoing liver resection at 15 centers. Patients were randomized (stratified by surgeon) at the conclusion of the liver resection surgery if general oozing was present that could not be controlled by further surgical methods and a topical hemostatic agent was needed to control the bleeding from the liver surface. For the primary endpoint, time to hemostasis, the fibrin sealant was shown to be statistically superior to the control hemostatic agents (5.3 minutes for EVICEL<sup>®</sup> versus 7.7 minutes for control; one-sided  $p=0.011$ ).

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

## 16 HOW SUPPLIED/STORAGE AND HANDLING

EVICEL<sup>®</sup> is supplied as a kit consisting of two separate packages:

- A package containing one vial each of BAC2 (55-85 mg/ml fibrinogen) and Thrombin (800-1200 IU/ml human thrombin) frozen solutions.
- A spray application device.

The different EVICEL<sup>®</sup> dosage forms include the following sizes (Table 7):

**Table 7: EVICEL<sup>®</sup> package sizes**

BAC2 Vial Size	Thrombin Vial Size	Package Size
1.0 ml	1.0 ml	2.0 ml
2.0 ml	2.0 ml	4.0 ml
5.0 ml	5.0 ml	10.0 ml

### **Storage and handling**

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

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

The two EVICEL<sup>®</sup> components, BAC2 and Thrombin, have been shown to be stable for up to 24 hours at room temperature.

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

Do not re-freeze EVICEL<sup>®</sup> once it has been thawed.

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

Discard if the packaging of EVICEL<sup>®</sup> is damaged.

Vials are for single use only. Discard unused contents.

## **17 PATIENT COUNSELING INFORMATION**

Because EVICEL<sup>®</sup> is made from human plasma, the physician should discuss the risks and benefits with the patient.

Instruct patients to consult their physician if symptoms of B19 virus infection (fever, drowsiness, chills, and runny nose followed about 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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