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------

DOSAGE AND ADMINISTRATION, Application Techniques (*2.3*)	04/2013-------
WARNINGS and PRECAUTIONS; Application Precautions (*5.1*)	04/2013------
ADVERSE REACTIONS, Clinical Trials Experience (*6.1*)	04/2013-------
ADVERSE REACTIONS, Post-Marketing Experience (*6.2*)	04/2013-------

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. Spray EVICEL® using only pressurized CO_2 gas. Apply a second layer if the hemostatic effect is not complete.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 modular spray application device which includes a 6 cm yellow flexible tip. Optional accessory tips are distributed seperatly.

The different EVICEL dosage strengths 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).*
- Do not use EVICEL® for spraying in endoscopic (intraluminal) procedures where the minimum recommended distance from the applicator tip to the target site cannot be assured *(2.3, 4.4).*

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

- Life-threatening air or gas embolism has occurred with the use of spray devices employing a 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 surface of the tissue (*5.1*).
- Monitor changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 when spraying EVICEL® due to the possibility of occurrence of gas embolism *(5.1).*
- To reduce the risk of potentially life-threatening gas embolism, spray EVICEL® using only pressurized CO2 gas at the recommended pressures and distances *(2.3).*
- Use EVICEL® spray application only if it is possible to accurately judge the spray distance, especially during laparoscopy *(2.3, 4.4).*
- Apply EVICEL® as a thin layer (2.3).
- Prior to applying EVICEL®, dry surface areas of the wound by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices*) (2.3).*
- Prepare and administer EVICEL® according to the instructions and with only devices recommended for this product *(2.3).*
- May carry a risk of transmitting infectious agents (e.g., viruses, the bacteria, parasites, variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the classic CJD agent *(5.2).*

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

Most common adverse reactions reported in clinical trials (≥5%) are bradycardia, nausea, hypokalemia, insomnia, hypotension, pyrexia, graft infection, vascular graft occlusion, peripheral edema, constipation (*6.1*).

Most common adverse reactions reported in post-marketing expierence are oedema, pyrexia, seroma, haematoma, tachycardia, dyspnoea, and urticaria (6.2).

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.**

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

No drug interactions are known.

See 17 for PATIENT COUNSELING INFORMATION

Revised: /2013

FULL PRESCRIBING INFORMATION: CONTENTS[1]

[1] Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

FOR TOPICAL USE ONLY – DO NOT INJECT

2.1 Thawing

Thaw the two components of EVICEL® (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® (BAC2 and Thrombin) within 30 days if refrigerated 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® once it has been thawed. Do not refrigerate EVICEL® after storage at room temperature. Discard unused product after 24 hours at room temperature.

Discard if the packaging of EVICEL® 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.

Prior to applying EVICEL®, dry surface areas of the wound by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices*)." (2.3)*

The 35 cm and 45 cm accessory tips should only be used by persons trained in laparoscopic, laparoscopic-assisted, endoscopic or open surgical procedures.

Prepare and administer EVICEL® according to the instructions and with only devices recommended for this product.

2.3 Application Techniques

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

Spray or drip EVICEL® 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® 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®, 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^2
2.0 ml	2.0 ml	4.0 ml	40 cm^2
5.0 ml	5.0 ml	10.0 ml	100 cm^2

Use standard surgical techniques for hemorrhagic control, including suture, ligature and cautery prior to the application of EVICEL®. Remove excess blood from the site of application to the extent possible using standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). Apply EVICEL ® with the application device supplied. EVICEL® 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®.
Vials are for single use only. Discard unused contents (see *HOW SUPPLIED/STORAGE and HANDLING* (*16*)).

<u>Application by Dripping</u>

a) Keep the tip of the applicator as close to the tissue surface as possible 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.

<u>Application by Spraying</u>

a) To reduce the risk of potentially life-threatening gas embolism, spray EVICEL® using only pressurized CO_2 gas at the recommended pressures and distances for each applicator tip. Connect the short gas tube on the application device to the luer-lock end of the long gas tube.

b) Connect the luer-lock of the gas tube (with the 0.2 μm filter) to a pressure regulator capable of delivering 15-25 psi (1.0-1.7 bar) of CO_2 pressure.

c) Ensure that gas pressure for open or laparoscopic procedures and specific accessory tips is set as indicated by the device manufacturer. The pressure regulator should be set as specified in Table 2 for each applicator tip (see *WARNINGS and PRECAUTIONS, Application Precautions* (*5.1*) *and ADVERSE REACTIONS, Post-Marketing* (*6.2*)).

d) Carefully monitor insufflation pressure in all laparoscopic procedures.

e) Ensure that the distance between the applicator tip head and the application bed is within the ranges recommended by the device manufacturer. Specific distances for open or laparoscopic surgery and for each applicator tip are defined in Table 2 (see *WARNINGS and PRECAUTIONS, Application Precautions* (*5.1*) *and ADVERSE REACTIONS, Post-Marketing* (*6.2*)).

Table 2: Application Parameters

Surgery	**Applicator tips to be used**	**Distance from target tissue**	**Spray pressure**
Open surgery	6 cm Yellow Flexible Tip	10-15 cm (4 – 6 in)	20-25 psi (1.4-1.7 bar)
	35 cm Black Rigid Tip		
	45 cm Yellow Flexible Tip		
Laparoscopic procedures	35 cm Black Rigid Tip	4 – 10 cm (1.6 – 4 in)	15 – 20 psi (1.0-1.4 bar)
	45 cm Yellow Flexible Tip	4-10 cm (1.6 – 4 inches)	20-25 psi (1.4-1.7 bar)

See instructions enclosed in the application device and accessory tip packages.

3 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 modular spray application device which includes a 6 cm flexible yellow tip. Optional accessory tips are distributed seperately.

The different EVICEL® dosage strengths include the following sizes (Table 3):

Table 3: EVICEL® 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® 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*)).

4.2 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*)).

4.3 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.

4.4 Spray Application

- Do not use EVICEL® for spraying in endoscopic (intraluminal) procedures where the minimum recommended distance from the applicator tip to the target site cannot be assured *(2.3, 4.4)*.

5 WARNINGS AND PRECAUTIONS

5.1 Application Precautions

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

To reduce the risk of potentially life threatening air embolism, spray EVICEL® using pressurized CO_2 gas only. For specific spray instructions on the recommended pressure and distance from tissue per type of surgical procedure and length of application tip, see Section 2.2.

Use EVICEL® spray application only if it is possible to accurately judge the distance from the spray tip to the tissue surface, especially during laparoscopy.

Monitor changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 when spraying EVICEL® due to the possibility of occurrence of gas embolism.

When using accessory tips with this product, follow the the instructions for use of the tips with attention to the spray pressure and distance ranges for each tip.

Prior to applying EVICEL®, dry surface areas of the wound by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices*).*

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5.2 Infection Risk from Human Plasma

Because EVICEL® is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, the bacteria, parasites, variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the classic 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

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.
The following adverse reactions which occurred during clinical studies were evaluated as having a possible causal relationship to treatment with EVICEL®. The frequency of all of the reactions listed below was common (defined as > 1/100, < 1/10).

Table 4: Adverse Reactions Clinical Trials Experience

MedDRA System Organ Class	**Preferred Term**
Adverse Reactions in Retroperitoneal or Intra-Abdominal Surgery Study	
Infections and infestations	Abdominal abscess
Adverse Reactions in Vascular Surgery Study	

Infections and infestations	Graft infection, Staphylococcal infection
Vascular disorders	Hematoma
General disorders and administration site conditions	Edema, peripheral
Investigations	Decreased hemoglobin
Injury, Poisoning and Procedural Complications	Incision site hemorrhage

Adverse Reaction Rates in Retroperitoneal or Intra-Abdominal Surgery Study
Among 135 patients undergoing retroperitoneal and intra-abdominal surgery (67 patients treated with EVICEL® and 68 controls), one abdominal abscess in the EVICEL® group and one abdominal and one pelvic abscess in the control group) were considered by the Sponsor to be possibly related to study treatment.

Adverse Reactions - Vascular Surgery
In a controlled study involving 147 patients undergoing vascular grafting procedures (75 treated with EVICEL® and 72 controls), nine patients experienced 12 adverse events that were assessed by the Sponsor as being possibly related to treatment. These included graft or staphylococcal infection, hematoma, incision site hemorrhage, peripheral edema, and decreased hemoglobin.

Adverse Reactions - Liver Surgery
In a controlled study involving 121 patients undergoing liver surgery (58 treated with fibrin sealant and 63 controls), no adverse reactions causally related to the study treatment were observed.

6.2 Post-Marketing Experience

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.

Post-marketing fatalities due to air embolism have been reported in association with the use of EVICEL® when applied using a spray device. These cases have occurred where EVICEL® was sprayed at a higher than indicated pressure for the device in use and when the spray tip was placed closer than the specified distance from the target site.

The following adverse reactions have been reported in post-marketing experience with EVICEL® and are categorized by MedDRA System Organ Class and Perferred Terms in order of decreasing frequency:

Table 5: Adverse Reactions Post-Marketing Experience

MedDRA System Organ Class	Preferred Term
General disorders and administration site conditions	Oedema, pyrexia
Injury, poisoning and procedural complications	Seroma
Vascular disorders	Haematoma
Infections and infestations	Abdominal abscess
Cardiac disorders	Tachycardia, cardiac arrest
Respiratory, Thoracic and Mediastinal disorders	Dyspnoea, pulmonary embolism
Skin and subcutaneous tissue disorders	Urticaria

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®. It is not known whether EVICEL® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. EVICEL® should be given to a pregnant woman only if clearly needed.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

The safety of EVICEL® 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® 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®, 4 patients treated with EVICEL® were age 16 years or younger. Of these, 2 were children age 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 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® is manufactured from pooled human plasma. EVICEL® 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 Grifols Therapeutics Inc., 155 Duryea Road, Melville, NY 11747 (License No. 1716).

Viral Clearance

Individual plasma units which are obtained for the production of EVICEL® 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 for Parvovirus B19 by NAT. Manufacturing pool testing, however, has a lower sensitivity than that of individual unit testing.

The manufacturing procedure for EVICEL® 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 5:

Table 6: 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 efficiency of the virus inactivation/removal procedures in reducing the level of 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 6:

Table 7: Results of virus removal/inactivation in validation studies

a) BAC2

Virus	HIV-1	BVDV	PRV	EMCV	HAV	CPV
Reduction factor (log_{10})						
SD Treatment	>4.4	>4.4	>4.0	Not Done	Not Done	0.0
Pasteurization	>4.4	>5.5	6.0	3.7	>5. 8	1.3
Global Reduction Factor	**>8.8**	**>9.9**	**>10.0**	**3.7**	**>5. 8**	**1.3**

b) Thrombin

Virus	HIV-1	SBV	BVDV	PRV	EMCV	HAV	CPV
	Reduction factor (log_{10})						
SD Treatment	>5.8	>5.3	>4.7	>4.3	Not Done	Not Done	0.0
Nanofiltration	>4.4	>5.3	Not Done	>5.5	6.4	7.0	5.9
Global Reduction Factor	**>10.2**	**>10.6**	**>4.7**	**>9.8**	**6.4**	**7.0**	**5.9**

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 sealant 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 polymerize and form a fibrin clot. Factor XIIIa, which is activated from Factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for FXIII activation by thrombin.

12.2 Pharmacodynamics

Pharmacodynamic studies were not conducted.
Clinical studies demonstrating hemostasis 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® 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 ^{125}I-thrombin it was shown that a slow absorption of biologically inactive peptides resulting from the breakdown of thrombin occurred, reaching a Cmax in the plasma after 6-8 hours. At the Cmax, 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 minor bleeding.

Fibrin sealants are metabolized 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® 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® 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® 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® 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® as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal or intra-abdominal surgery, EVICEL® was shown to be superior to the control product (Surgicel®, oxidized regenerated cellulose) in achieving hemostasis in less than 10 minutes (see Table 7). Superiority was also established at the secondary efficacy endpoints of 7 and 4 minutes.

Table 8: Efficacy results in retroperitoneal and intra-abdominal surgery

Variable	EVICEL® 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 EVICEL® 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 8).

Table 9: Efficacy results in vascular surgery

Number (%) of patients achieving hemostasis	EVICEL®	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® 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® 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® 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 strengths include the following sizes (Table 9):

Table 10: EVICEL® 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

The vials must be stored in an upright position.

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® 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® once it has been thawed.

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

Discard if the packaging of EVICEL® is damaged.

Vials are for single use only. Discard unused contents.

17 PATIENT COUNSELING INFORMATION

Because EVICEL® 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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