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)

Kit consisting of 1 vial of BAC2 (55-85 mg/ml fibrinogen) and 1 vial of Thrombin (800-1200 IU/ml human thrombin)

For topical use only

Initial U.S. approval: 2003

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

INDICATIONS AND USAGE, General adjunct to hemostasis in surgery (*see 1*) 1/2008

DESCRIPTION, HAV reduction factor for the pasteurization of BAC2 (*see 11*) 6/2007

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

- Adjunct to hemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques is ineffective or impractical.

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

- For topical use only. Do not inject directly into the circulatory system.
- The two components of EVICEL, BAC2 and Thrombin are to be thawed prior to usage (*see 2.1*). The time between thawing and application is restricted to 24 hours at room temperature or 30 days of refrigeration (*see 16*).
- EVICEL Fibrin Sealant (Human) should be sprayed or dripped onto the tissue in short bursts (0.1-0.2 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 upon the area of tissue to be treated and the method of application (*see 2.2*).
- Vials are for single use only. Discard unused contents.

-------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 use in individuals known to have anaphylactic or severe systemic reaction to human blood products.**
- **Do not use for the treatment of severe or brisk arterial bleeding.**

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

- 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 (*see 11*).

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

In liver surgery, bradycardia occurred more frequently in the fibrin sealant group (*see 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.**

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

No drug interactions are known.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2008

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 is ineffective or impractical.

2 DOSAGE AND ADMINISTRATION

2.1 Thawing and preparation prior to application

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.

Unopened vials can be refrigerated for up to 30 days.

The two EVICEL components 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 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 biologics 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) Care should be taken when removing the vial assembly. It should be a gentle rotation to ensure valve engagement.

2.2 Application techniques

EVICEL is used topically and should be applied on the surface of bleeding tissue only. Do not inject directly into the circulatory system.

EVICEL can be sprayed or dripped onto the tissue in short bursts (0.1-0.2 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 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 the following table:

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

Standard surgical techniques for hemorrhagic control, including suture, ligature and cautery, should be used prior to the application of EVICEL. Excess blood should be removed from the site of application if possible, although a dry field is not essential, EVICEL should then be applied 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.

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 to 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, the catheter tip can be wiped clean or cut 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 20-25 psi of pressure.

c) The pressure regulator should be used in accordance with the manufacturer's instructions.

d) An air pressure of 20-25 psi (measured by airflow) should be used for spraying.

e) The distance between the nozzle and the tissue surface should ideally be between 10 and 15 cm during spraying.

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 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

4 CONTRAINDICATIONS

- Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products.
- Do not use for the treatment of severe or brisk arterial bleeding.

5 WARNINGS AND PRECAUTIONS

- Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. 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.

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%). However, it should be noted that 68 comparisons of adverse events would be expected to yield approximately three adverse events with $p<0.05$ by chance alone.

7 DRUG INTERACTIONS

No drug interactions are known.

8 USE IN SPECIFIC POPULATIONS

8.1 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 due to the human origin of its components. However, studies to evaluate the potential reproductive/developmental toxicity of Triton and TNBP were conducted in animals and are summarized in the Non Clinical Toxicology section (13).

8.4 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.

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

11 DESCRIPTION

EVICEL is manufactured from pooled human source 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.

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 highly purified human thrombin that activates clotting of the final combined product. Thrombin is a highly 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 source plasma that is obtained from US licensed plasma collection centers. Cryoprecipitate manufacture may be performed by Precision Pharma Services, Inc., 155 Duryea Road, Melville, NY 11747 (License No. 1633).

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, and must be negative (non-reactive).

Additionally the plasma is tested by NAT for HAV and HBV. 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 source plasma, each manufacturing pool is tested for HBsAg, HIV-1 & 2 Ab, HCV Ab, and HCV 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 below:

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 the following table:

a) BAC2

Virus	**HIV-1**	**BVDV**	**PRV**	**EMCV**	**HAV**	**CPV**
Reduction factor (log_{10})						
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	**>8.81**	**>9.85**	**>3.96**	**3.69**	**>5.78**	**1.33**

b) Thrombin

Virus	**HIV-1**	**SBV**	**BVDV**	**PRV**	**EMCV**	**HAV**	**CPV**
	Reduction factor (log_{10})						

SD Treatment	>5.82	>5.31	>4.74	>4.25	Not Done	Not Done	0.0
Nanofiltration	>4.36	>5.32	Not Done	>5.47	6.37	6.95	5.85
Global Reduction Factor	**>10.18**	**>10.63**	**>4.74**	**>9.72**	**6.37**	**6.95**	**5.85**

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

12 CLINICAL PHARMACOLOGY

Thrombin is a highly specific protease that transforms the fibrinogen contained in BAC2 into fibrin. Thrombin is partly adsorbed by the fibrin so formed. Excess thrombin, if any, is inactivated by protease inhibitors in the blood. In a study to evaluate the blood levels of ^{125}I thrombin after application of EVICEL to hepatic wounds in rabbits, it was determined that excess thrombin is complexed with anti-thrombin. The study results verify that systemic exposure to thrombin is approximately equivalent to that generated by a minor hemorrhage and is not expected to pose an increased risk of thromboembolism**.** The study results show that thrombin is absorbed systemically when administered directly to a hepatic wound, but the systemic exposure is minimal.

13 NONCLINICAL TOXICOLOGY

EVICEL has been classified as non-irritant in the Primary Cutaneous Irritation Test and slightly irritant in the Ocular Irritation test. Neither BAC2 nor Thrombin solution induces mutagenic effects in the Ames test.

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

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

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.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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. The effect of EVICEL on fertility has not been evaluated.

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.

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 below). Superiority was also established at the secondary efficacy endpoints of 7 and 4 minutes.

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 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 in favor of the treatment group, with 83.3% of the test subjects versus 39.7% of control subjects achieving hemostasis by 4 minutes.

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 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

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 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 at room temperature. Discard unused product after 24 hours at room temperature.

Discard if the packaging of EVICEL is damaged.

17 PATIENT COUNSELING INFORMATION

Some viruses such as hepatitis A virus and parvovirus B19 are particularly difficult to remove or inactivate. Parvovirus B19 most seriously affects pregnant women, or immune-compromised individuals. Symptoms of parvovirus B19 infection include fever, drowsiness, chills, and runny nose followed about two weeks later by a rash and joint pain. Evidence of hepatitis A may include several days to weeks of poor appetite, fatigue and low-grade fever followed by nausea, vomiting and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

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