PRODUCT MONOGRAPH

EVICEL®

2 x 1 mL, 2 x 2 mL & 2 x 5 mL Kits

Fibrin Sealant Kit Ph. Eur.

Haemostatic Agent

Component	**Human Clottable Protein:**	**Human Thrombin:**
Strength	50- 90 mg/mL	800-1200 IU/mL
Factor XIII	2-15 IU/mL	
Dosage Form	Single use kits consisting of one vial each of frozen sterile solutions of Human Clottable Protein and Thrombin	

Sponsor Name: Omrix Biopharmaceuticals Ltd.

Sponsor Address: MDA Blood Bank,
Sheba Hospital, Ramat-Gan
POB 888, Kiryat Ono 5510801
ISRAEL

Importer/Distributor:
Johnson & Johnson Medical Products
200 Whitehall Drive
Markham, Ontario
L3R 0T5
CANADA

Submission Control No: 208336 Date of Approval: October 13, 2017

Table of Contents

EVICEL
Fibrin Sealant Kit Ph. Eur.

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Dosage Form	Single use kits consisting of one vial each of frozen sterile solutions of Human Clottable Protein and Thrombin. Supplied as Kits of 2 x 1 mL, 2 x 2 mL or 2 x 5 mL	
Strength	**Component 1 (Clottable Protein):** Concentrate of human clottable protein (50-90 mg/mL)	**Component 2 (Thrombin):** Human thrombin (800 – 1200 IU/mL)
Non-medicinal Ingredients	Arginine Hydrochloride Glycine Sodium Citrate Sodium Chloride Calcium Chloride Water for Injections	Calcium Chloride Human Albumin Mannitol Sodium Acetate Water for Injections
Route of Administration	For topical use	
Clinically relevant excipients		Human Albumin 5.0-6.5 mg/mL Mannitol 18.5-20.5 mg/mL

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 Human Clottable Protein and one vial of Thrombin. The second package contains a sterile application device and optional accessory tips (that are supplied separately). The two components (Human Clottable Protein and Thrombin) should be mixed and applied topically.

The Human Clottable Protein and Thrombin components appear as white to slightly yellowish opaque frozen mass. The thawed preparation is clear and colourless to slightly yellowish. The components contain no preservatives.

The Human Clottable Protein component is a sterile solution, pH 6.7-7.2, which consists mainly of a concentrate of human fibrinogen. Fibrinogen is a plasma-derived product that forms a clot when combined with thrombin. The composition of the Human Clottable

Protein solution is as follows: Human clottable protein (50-90 mg/mL), arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, water for injections (WFI).

The Thrombin component 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 Human Clottable Protein into fibrin. The composition of the Thrombin solution is as follows: Human thrombin (800 - 1200 IU/mL), calcium chloride, human albumin, mannitol, sodium acetate, water for injections (WFI).

The Cryoprecipitate, which is the starting material for Human Clottable Protein, and the 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.

Individual plasma units which are obtained for the production of EVICEL are tested for HBsAg, anti-HIV I/II, anti-HCV, and Syphilis. Mini-pools are NAT tested for HAV, HBV, HIV-1, HCV, and Parvovirus B19. Specifications for these tests require a negative result for HAV, HBV, HIV-1 and HCV, and not exceeding 10^4 IU/mL parvovirus B19. The plasma pools are tested for HBsAg, anti-HIV I/II and NAT tested for HCV as described in the table below.

Test	**Test Performed on :**		
	Individual Donation (Qualtex)	**Mini-pool (up to 512 donations) (NGI)**	**Plasma pool**
HBsAg	X		X (Sanquin)
HIV 1 and 2 Antibody	X		X (Sanquin)
HCV Antibody	X		
HCV RNA		X	X (NGI)
HIV RNA		X	
HBV DNA		X	
HAV RNA		X	
B19 DNA		X	
Other Tests			
Syphilis (4-monthly only)	X		

The manufacturing procedure for EVICEL includes processing steps which are designed to reduce the risk of viral transmission. In particular, both Human Clottable Protein and Thrombin undergo two discrete virus inactivation/removal steps, summarized below:

Step	Component	
	Human Clottable Protein	**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

INDICATIONS AND CLINICAL USE

EVICEL is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. Evidence of efficacy and safety has been demonstrated in the following clinical trials:

1. Liver surgery such as liver resection and reduced-size liver transplantation.
2. Orthopedic surgery such as total hip replacement and total knee replacement.
3. Retroperitoneal/intra-abdominal surgery.
4. Vascular surgery.

In addition, EVICEL is indicated for suture line sealing in dura mater closure. (See Use in Neurosurgery)

Geriatric Use (> 65 years of age)

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.

Pediatric Use

Data are too limited to support the safety and effectiveness of EVICEL in children. Of 135 patients undergoing retroperitoneal and intra-abdominal surgery who were included in the controlled study of EVICEL, 4 patients treated with EVICEL were aged 16 years or younger. Of these, 2 were children aged 2 and 5 years and 2 were adolescents of 16 years. No data are currently available for ages younger than 2 years.

CONTRAINDICATIONS

EVICEL is contraindicated in:

- Individuals known to have anaphylactic or severe systemic reaction to human blood products.

- Injection directly into the circulatory system. EVICEL must not be applied intravascularly. Intravascular application of EVICEL may result in life-threatening thromboembolic events.

Do not use EVICEL for treatment of severe or brisk arterial bleeding.

The spray application of EVICEL should not be used in endoscopic (intra luminal) procedures. For laparoscopy, see sections Warnings and Precautions, and Method of Application by Spraying.

WARNINGS AND PRECAUTIONS

WARNINGS

When medicinal products manufactured from human plasma are administered, the possibility of transmission of infective agents cannot be totally excluded. The physician should discuss the risks and benefits of administering this product with the patient, before prescribing or administering to the patient (see Warnings-General).

Life-threatening/fatal air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants including 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. To reduce the risk of potentially life threatening air embolism EVICEL should be sprayed using pressurized CO_2 gas only. (See Method of Application by Spraying)

General

- EVICEL is intended for topical use only. Do not apply intravascularly. Life threatening thromboembolic complications may occur if the product is unintentionally applied intravascularly.

- As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, and tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, administration should be immediately discontinued. In case of shock, standard medical treatment for shock should be implemented.

- Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infections agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

  The measures taken are considered effective for enveloped viruses such as HIV, Hepatitis C Virus and Hepatitis B Virus and for the non-enveloped virus Hepatitis A Virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

  It is strongly recommended that every time EVICEL is administered to a patient, the name and the batch number of the product are recorded to maintain a link between the patient and the batch of the product.

Application Precautions

- Before administration of EVICEL, care is to be taken that parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites.

- EVICEL spray application should only be used if it is possible to accurately judge the spray distance, especially during laparoscopy. (See Method of Application by Spraying)

- When using accessory tips with this product, the instructions for use of the tips should be followed with attention to the spray pressure and distance ranges for each tip. (See Method of Application by Spraying)

- EVICEL should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

- When spraying EVICEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

Special populations

Pregnant or nursing women

The safety of fibrin sealants/haemostatics for use in human pregnancy, during labor and delivery or during breast-feeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and post-natal development.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

Geriatric Use (> 65 years of age)

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.

Pediatric Use

Data are too limited to support the safety and effectiveness of EVICEL in children. Of 135 patients undergoing retroperitoneal and intra-abdominal surgery who were included in the controlled study of EVICEL, 4 patients treated with EVICEL were aged 16 years or younger. Of these, 2 were children aged 2 and 5 years and 2 were adolescents of 16 years. No data are currently available for ages younger than 2 years.

Use in Tissue Gluing, Endoscopy or Gastro-Intestinal Anastomoses

Adequate data are not available to support the use of this product in tissue gluing, application through an endoscope for treatment of bleeding or in gastro-intestinal anastomoses.

Use in Neurosurgery

EVICEL should not be used:

- For sealing the suture line in dura mater if there are gaps of greater than 2mm after suturing
- As a glue for the fixation of dural patches
- As a sealant when the dura mater cannot be sutured

Adequate data are not available to support the use of EVICEL in the following situations as they have not been evaluated in randomized clinical trials:

- In patients undergoing radiotherapy within 7 days after surgery. It is not known whether radiation therapy could affect the efficacy of fibrin sealant when used for suture line sealing in dura mater closure.

- As a sealant in transphenoidal and otoneurosurgical procedures

- Concomitant use of EVICEL with implants from synthetic materials or dural patches for dural suture line sealing

Complete haemostasis should be achieved before application of EVICEL to seal the dural suture line.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions which may be reported in association with fibrin sealants are described below. Since no such reactions have been reported during clinical trials with EVICEL, the frequency of these events with EVICEL is not known.

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatics. In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product. Mild reactions can be managed with anti-histamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

Antibodies against components of fibrin sealant/haemostatic products may occur rarely.

Inadvertent intravascular injection could lead to thromboembolic event and disseminated intravascular coagulation, and there is also a risk of anaphylactic reaction.

Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following adverse reactions in retroperitoneal or intra-abdominal surgery and in neurosurgery was common (defined as > 1/100, < 1/10). The frequency of all of the adverse reactions in vascular surgery was uncommon (defined as ≥ 1/1000, <1/100).

MedDRA System Organ Class	**Preferred Term**	**Frequency**
Adverse Reactions in Retroperitoneal or Intra-Abdominal Surgery Study		
Infections and infestations	Abdominal abscess	Common
Adverse Reactions in Vascular Surgery Study		
Infections and infestations	Graft infection, Staphylococcal infection	Uncommon
Vascular disorders	Haematoma	Uncommon
General disorders and administration site conditions	Oedema peripheral	Uncommon
Investigations	Decreased haemoglobin	Uncommon
Injury, Poisoning and Procedural Complications	Incision site haemorrhage	Uncommon
	Vascular graft occlusion/vascular graft thrombosis	Uncommon
	Wound	Uncommon
	Post procedural haematoma	Uncommon
	Post-operative wound complication	Uncommon
Adverse Reactions in Neurosurgery Study		
Infections and Infestations	Meningitis	Common
Nervous System Disorders	Intracranial hypotension (CSF leakage)	Common
	CSF rhinorrhoea	Common
	Headache	Common
	Hydrocephalus	Common
	Subdural hygroma	Common
Vascular Disorders	Haematoma	Common

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), no adverse events were considered to be causally related to the study treatment according to the investigator assessments. However, 3 serious adverse events (SAE) (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), a total of 16 subjects were reported to have had a graft thrombosis/occlusion adverse event during the study period. The events were evenly distributed across treatment arms, with 8 each in the EVICEL and the control groups.

A prospective, non-interventional safety study was conducted which involved 300 patients undergoing vascular surgery during which EVICEL was used. Safety monitoring focused on the specific adverse reactions of graft patency, thrombotic events, and bleeding events. No adverse reactions were reported during the study.

Adverse Events Rates in Liver Surgery Studies

68 types of adverse event were reported for at least 5% of the patients in either treatment group in two controlled studies conducted in liver surgery. Seven showed a statistically significant difference between treatments (two-sided $p < 0.05$, Mantel-Haenszel chi-squared test). Of these only bradycardia was more frequent in the Crosseal group than in the control group (9.5% versus 2.5%, $p = 0.041$). Gall bladder disorder (which included bile leakage, biliary stenosis, and biliary tract surgery) was less frequent in the Crosseal group than in the control group (9.5% versus 21.3%, $p = 0.002$). However, it should be noted that 68 comparisons of adverse events would be expected to yield approximately three with $p < 0.05$ by chance alone.

Adverse Events – Out Of A List Of 68 Events Which Were Reported For At Least 5% Of The Patients In Either Treatment Group - For Which There Was Evidence Of A Difference In Frequency Between The Crosseal And Control Groups In Studies Of Liver Surgery

Body System	Adverse Event	Crosseal (N = 74)	Control (N = 80)	P Value[a]
Gastrointestinal	Diarrhoea	9 (12.2%)	17 (21.3%)	0.032
	Nausea	29 (39.2%)	39 (48.8%)	0.046
Heart rate and rhythm	Bradycardia	7 (9.5%)	2 (2.5%)	0.041
Liver and biliary	Gall bladder disorder	7 (9.5%)	17 (21.3%)	0.002
Red blood cell	Anaemia	17 (23%)	23 (28.8%)	0.029
Respiratory	Bronchitis	1 (1.4%)	5 (6.3%)	0.030
	Rhinitis	2 (2.7%)	5 (6.3%)	0.026

[a] Mantel-Haenszel chi-squared test.

In results of controlled studies, 18 out of 74 patients in the Crosseal group (24%) and 22 of 80 patients (28%) in the control group had one or more serious adverse events. The

most frequent serious adverse events in the Crosseal group were sepsis (4 cases, 5.4%) and moniliasis (3 cases, 4.1%). Serious adverse events in the Crosseal group were not considered to be probably or possibly related to Crosseal.

Adverse Event Rates in Joint Replacement Studies

Twenty-two adverse events were reported for at least 5% of the patients in either treatment group in the controlled studies in joint replacement. Two showed a statistically significant difference between treatments (two-sided $p < 0.05$, Mantel-Haenszel chi-squared test). Of these, nausea and anaemia were less frequent in the Crosseal group than in the control group (29.3% versus 45.5%, and 26.1 % versus 34.7%, $p = 0.046$ and 0.029 respectively).

Adverse Events – Out Of A List Of 22 Events Which Were Reported For At Least 5% Of The Patients In Either Treatment Group - For Which There Was Evidence Of A Difference In Frequency Between The Crosseal And Control Groups In Studies Of Joint Replacement

Body System	Adverse Event	Crosseal (N = 92)	Control (N = 101)	P Value[a]
Gastrointestinal	Nausea	27 (29.3%)	46 (45.5%)	0.046
Red blood cell	Anaemia	24 (26.1%)	35 (34.7%)	0.029

[a] Mantel-Haenszel chi-squared test.

In results of controlled studies, 8 out of 92 patients in the Crosseal group (8.7%) and 10 of 101 patients (9.9%) in the control group had one or more serious adverse events. None of the serious adverse events in joint replacement was considered to be probably or possibly related to study treatment.

Adverse Reactions – Neurosurgery

In a controlled study involving 139 patients undergoing elective neurosurgical procedures (89 treated with EVICEL and 50 controls), a total of 7 subjects treated with EVICEL experienced nine AEs and in the control group 2 subjects experienced three AEs that were considered to be possibly related to the study product. These included intracranial hypotension (CSF leakage), CSF rhinorrhea, meningitis, headache, hydrocephalus, subdural hygroma, and haematoma.

The incidence of CSF leakage and the incidence of Surgical Site Infections were monitored as safety endpoints in the study. At 30 days post-operatively the incidence of SSIs was similar between the two treatment groups. Post-operative CSF leakage occurred within 30 days from treatment in 2/89 (2.2%) subjects treated with EVICEL. Including the two cases of rhinorrhoea, overall CSF leak rate was 4.5% (4/89) in subjects treated with EVICEL and 2.0% (1/50) in subjects treated with additional sutures.

Post-Market Adverse Drug Reactions

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

Immune system disorders: anaphylactic responses, hypersensitivity

Cardiovascular disorders: bradycardia, tachycardia, cardiac arrest, hypertension

Respiratory, thoracic and mediastinal disorders: dyspnea, tachypnea, hyperventilation

Thromboembolic events

Skin and subcutaneous tissue disorders: urticaria

General disorders and administration site conditions: edema, pyrexia

Injury, poisoning and procedural complication: seroma

Air or gas embolism: Post- marketing fatalities reported in association with the use of EVICEL when spraying the product at higher than recommended pressures and/or in closer than recommended distances.

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

DRUG INTERACTIONS

No formal interaction studies have been performed. Similar to comparable products or thrombin solutions, the product may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.

DOSAGE AND ADMINISTRATION

For topical use. The product should only be prepared and administered according to the instructions and with the devices recommended for this product.

Before administration of EVICEL, care is to be taken that parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites. The surface area of the wound should be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).

The amount of EVICEL that will be applied depends on the surface area of tissue to be treated during the operation. It will be dripped onto the tissue in short bursts or sprayed in very small amounts (0.1-0.2 mL), to produce a thin, even layer. If application of a single layer of EVICEL does not completely stop the bleeding, a second layer may be applied.

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:

EVICEL Package Size	Area of Coverage with Layer of 1 mm Thickness
2x1.0 mL	20 cm^2
2x2.0 mL	40 cm^2
2x5.0 mL	100 cm^2

Recommended Dose

The volume of EVICEL to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualised by the treating physician. In clinical trials in vascular surgery, the individual dosage used was up to 4 mL; for suture line sealing in dura mater closure, doses of up to 8mL were used, whereas in retroperitoneal or intra-abdominal surgery the individual dosage used was up to 10 mL. However, for some procedures (e.g. liver traumata) larger volumes may be required.

The initial volume of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

Administration

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

- A package containing one vial each of Human Clottable Protein (50-90 mg/mL human clottable protein) and Thrombin (800-1200 IU/mL human thrombin) frozen solutions.

- An application device and optional appropriate accessory tips (that are supplied separately).

The two components (Human Clottable Protein and Thrombin) should be thawed and administered by spraying or dripping directly onto the surface of the tissue to be treated, using the EVICEL application device. This device allows equal amounts of the two components to be applied simultaneously, and ensures mixing of the components, which is essential for the sealant to achieve optimal efficacy.

Thawing

Thaw the two components of EVICEL (Human Clottable Protein and Thrombin) in one of the following ways:

- **2-8°C** (refrigerator): vials thaw within 1 day, or
- **20-25°C** (room temperature): vials thaw within 1 hour, or
- **37ºC** (e.g. water bath, using aseptic technique, or by warming vials in the hand): vials thaw within 10 minutes and must not be left at this temperature for longer than 10 minutes or until fully thawed. The temperature must not exceed 37ºC.

Before use, the product must reach 20-30°C.

Vials thawed at room temperature or above should be used within 24 hours and not returned to refrigerated storage.

Preparation

EVICEL should be applied using the EVICEL application device and optional use of a tip accessory to the device. Leaflets giving detailed instructions for use of EVICEL in conjunction with the application device and optional accessory tips are provided with in the package of the application device and of the accessories.

The use of EVICEL is restricted to experienced surgeons who have been trained in the use of EVICEL.

a) Draw the contents of the two vials into the two sterile syringes (see diagram enclosed in the application device package).

b) Fill both syringes of application device with equal volumes. The solutions should not contain air bubbles.

c) Caution should be taken when twisting vials off. It should be a gentle manoeuvre to ensure valve engagement.

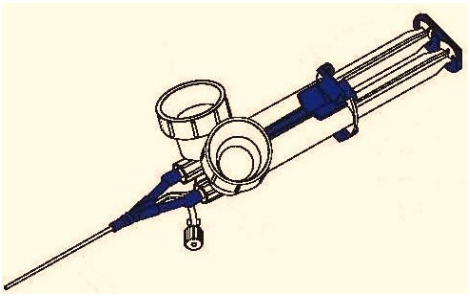
Method of Application by Dripping

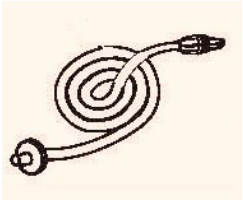
Keeping the tip of the applicator as close to the tissue surface as possible, but without touching the tissue during application, apply individual drops to the area to be treated. The drops should be allowed to separate from each other and from the tip of the

applicator. If the applicator tip becomes blocked, the catheter tip can be cut back in 0.5 cm increments.

Method of Application by Spraying

To reduce the risk of life-threatening air embolism, EVICEL should only be sprayed using pressurised CO_2 at the pressures and distances indicated for each applicator tip (see table below).





➔ Gas tube connects to the short air tube

Connects to ➔
Pressure Regulator

a) Connect the short air tube on the application device to the male luer-lock end of the long gas tube.

b) Connect the female luer-lock of the air 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) When applying EVICEL using a spray device, be sure to use only the pressure within the range recommended by the spray device manufacturer. Do not spray at a distance closer than the recommended by the spray device manufacturer.

Surgery	**Applicator tips to be used**	**Recommended distance from target tissue**	**Recommended 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 in)	20 psi (1.4 bar)

d) The product should then be sprayed onto the surface of the tissue in short bursts (0.1-0.2 mL) to form a thin, even layer. EVICEL forms a clear film over the area of application.

e) When spraying EVICEL, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

OVERDOSAGE

No case of overdose has been reported.

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacodynamics

No pharmacodynamic studies have been performed with EVICEL.

Pharmacokinetics

Since EVICEL is intended for topical use only (i.e. for direct application onto tissue during surgery) and intravascular administration is contraindicated, intravascular pharmacokinetic studies have not been performed in man.

STORAGE AND STABILITY

Vials must be stored in an upright position.

Store frozen at ≤ -18°C, protected from light. If thawed, do not refreeze. EVICEL is stable for 2 years from the date of production and should not be used after the expiry date printed on the carton.

After thawing, the thaw date should be noted on the carton. Unopened vials can be stored at 2-8°C in their cartons bearing the thaw date and protected from light, for up to 30 days, without being frozen again during this period. The thawed product should be used within 30 days from the thaw date or the product expiry date, whichever comes first. At the end of this period and/or after 24 hours at 25±2°C, unused product must be discarded.

Once drawn up into the application device, product must be used immediately.

DOSAGE FORMS, COMPOSITION AND PACKAGING

EVICEL is supplied as a package containing two separate vials (glass type I) with rubber stoppers (type I), each containing 1 mL, 2 mL or 5 mL solution of Human Fibrinogen and Human Thrombin, respectively. An application device and appropriate accessory tips are supplied separately.

Fibrinogen (50-90 mg/mL) is a concentrate of clottable protein and Thrombin (800-1200 IU/mL) is an enzyme that causes clottable protein to coalesce. Thus, when the two components are mixed together they clot instantly.

EVICEL is applied during surgical operations, to reduce bleeding and oozing during and after the operation. It is dripped or sprayed onto cut tissue where it forms a thin layer that seals the tissue and stops bleeding.

EVICEL can also be used in blood vessels surgery and in surgery taking place in the area between the bowels and the posterior abdominal wall.

Fibrinogen and Thrombin should be thawed and administered by spraying or dripping directly onto the surface of the tissue to be treated, as described under Dosage and Administration. The application device allows equal amounts of the two components to be applied simultaneously, and ensures that they mix evenly, which is important for the sealant to have its optimal effect.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

- **Proper name:** Fibrin Sealant Kit
- **Chemical name:** Not applicable
- **Molecular formula:** Not applicable
- **Molecular mass:** Human fibrinogen: 340 KD, human α-thrombin 35 – 39 KD.
- **Structural formula:** Not applicable
- **Physicochemical properties:** Solutions for sealant, light sensitive, heat labile

Product Characteristics

Cryoprecipitate, the starting material for Human Clottable Protein, and cryo-poor plasma, the starting material for the production of Thrombin are made from pooled human plasma obtained from US licensed plasma collection centres.

Fibrinogen:

Human Clottable Protein 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. The SD reagents are removed, and the preparation is subsequently treated by pasteurization.

Prior to pasteurization stabilizers are added. After pasteurization, the stabilizers used for heat treatment are removed by diafiltration and the product is concentrated. 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:

Thrombin is manufactured by chromatographic purification of pro-thrombin 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 to inactivate lipid enveloped viruses.

The SD reagents are removed and stabilizers are added prior to 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.

Viral Inactivation

Individual plasma units which are obtained for the production of EVICEL are tested for HBsAg, anti-HIV I/II, anti-HCV, and Syphilis. Mini-pools are NAT tested for HAV, HBV, HIV-1, HCV, and Parvovirus B19. Specifications for these tests require a negative result for HAV, HBV, HIV-1 and HCV, and not exceeding 10^4 IU/mL parvovirus B19. The plasma pools are tested for HBsAg, anti-HIV I/II and NAT tested for HCV and as described in the table below.

Test	**Test Performed on :**		
	Individual Donation (Qualtex)	**Mini-pool (up to 512 donations) (NGI)**	**Plasma pool**
HBsAg	X		X (Sanquin)
HIV 1 and 2 Antibody	X		X (Sanquin)
HCV Antibody	X		
HCV RNA		X	X (NGI)
HIV RNA		X	
HBV DNA		X	
HAV RNA		X	
B19 DNA		X	
Other Tests			
Syphilis (4-monthly only)	X		

The manufacturing procedure for EVICEL includes processing steps which are designed to reduce the risk of viral transmission. In particular, both Human Clottable Protein and Thrombin undergo two discrete virus inactivation/removal steps, summarized below:

Step	**Component**	
	Human Clottable Protein	**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

The efficacy of these procedures in inactivating a range of viruses has been assessed. The viruses used for validation studies were selected to give a range of physico-chemical

characteristics and the results of the validation studies are summarized in the following table:

a) Human Clottable Protein

Virus	HIV-1	BVDV	PRV	EMCV	HAV	CPV	MVM
Reduction factor (log_{10})*							
SD Treatment	>4.4	>4.4	>4.0	Not Done	Not Done	0.0	Not Done
Pasteurization	>4.4	>5.5	Not Done	3.7	>5.8	1.3	Not Done
Immune neutralisation plus filtration	Not tested	Not tested	Not tested	Not tested	>3.5	Not tested	Not tested
Global Reduction Factor	**>8.8**	**>9.9**	**>4.0**	**3.7**	**>5.8**	**1.3**	Not Done

***Rounded values**

b) Thrombin

Virus	HIV-1	SBV	BVDV	PRV	EMCV	HAV	CPV	MVM
Reduction factor (log_{10})*								
SD Treatment	>5.8	>5.3	>4.7	>4.3	Not Done	Not Done	0.0	Not Done
Nanofiltration	>4.6‡	Not Done	>5.6	>5.7‡	>7.4	>7.6	Not Done	>6.7
Global Reduction Factor	**>10.4**	**>5.3**	**>10.3**	**>10.0**	**>7.4**	**>7.6**	**0.0**	**>6.7**

***Rounded values**

‡Taking into account the virucidal effect of the starting material

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

MVM: Murine Minute virus

CLINICAL TRIALS

Study demographics and trial design

Table 1 Summary of EVICEL Study 400-05-006 in Soft Tissue Bleeding and EVICEL Study 400-05-001 in Vascular Surgery.

Study #	Trial Design	Dosage and duration	Number of Patients Treatment/Control	Mean Age (Range)	Gender (M/F)
400-05-006	Phase III, prospective, randomised controlled clinical study to evaluate the safety and efficacy of EVICEL.	Application of two 5mL kits of EVICEL (2 mL each of Human Fibrinogen and Thrombin [total 8mL])	66/69	55.1 (16-75)	57 F 78 M
400-05-001	Phase III, multicentre, prospective, randomised, controlled, parallel group	Application of one kit of EVICEL (2 mL each of Human Fibrinogen and Thrombin [total 4 mL])	75/72	66.0 (17-75)	70 F 77 M

Table 2 Summary of Patient Demographics for Trials in Liver Surgery

Study #	Trial Design	Dosage and Duration	Number of Patients Treatment/Control	Mean Age (Range)	Gender (M/F)
Q LIV 008 US	Phase III Single-blind, randomized, standard-treatment active controlled, parallel-group, multicentre study.	Application of up to 10 mL (mean 7.9 mL)	58/63	57 (19–79)	52F; 69M
OFI LIV 003 B	Phase II open label, active controlled, non-randomized, comparative clinical study	Application of 1-2 mL per 100cm^2 cut surface (mean 3.4 mL)	17/17	16.5 (<1 -37)	13F; 21M
OFI LIV 002 UK	Phase II open, non comparative, prospective study	Application of 1-2 mL per 100cm^2 cut surface, (mean 12.4 mL) No control	21/0	58 (2 - 80)	9F; 12M

Table 3 Summary of Patient Demographics for Trials in Orthopaedic Surgery

Study # (Ref.)	Trial Design	Dosage and duration	Number of Patients		Mean Age (Range) Years		Gender (M/F)	
			Crosseal	Control	Crosseal	Control	Crosseal	Control
Q THR 009 US	Phase III single-blind, randomized, parallel group standard treatment controlled, multicenter study	Application of up to 10 mL (mean 9.5 mL)	54	43	67 (34-84)	68 (40-88)	24F; 30M	20F; 23M
OFI TKR 001 IL (1)	Phase II single-blind randomized parallel group standard treatment control multicentre study	Application of 10 – 20 mL (mean 17.6 mL)	29	30	70 (62 -82)	70 (47-83)	22F 7M	24F 6M
OFI TKR 004 US (2)	Phase III single blind, randomized, parallel group, standard treatment control multicentre study	Application of up to 10 mL (mean 10 mL).	25	28	68 (41- 86)	69 (43-85)	12F; 13M	17F; 11M
OFI THR 005 UK (3)	Phase II open pilot study comparing three regimens of administration of Crosseal in THR. Comparison with matched historical controls.	Application of up to 10 mL (mean 9.8 mL).	13	0	68 (50-83)	N/A	8F; 5M	N/A

Table 4 Summary of Patient Demographics in Neurosurgery (Study 400-09-001)

Study #	Trial Design	Dosage and duration	Number of Patients Treatment/Control	Median Age (Range)	Gender (M/F)
400-09-001	Phase III, multicentre, prospective, randomised, controlled study.	Application of up to 8mL (two 2 mL kits of EVICEL)	89/50	56 (20-78)	72 F 67 M

Study Results

Clinical Trial in Soft Tissue Bleeding (Study 400-05-006)

This was a phase III, prospective, randomised controlled clinical study to evaluate the safety and efficacy of EVICEL. Efficacy was evaluated by the assessment of whether EVICEL was non-inferior to Surgicel® in achieving haemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery. Surgicel®, is an oxidized, regenerated cellulose haemostat.

Table 5. Results of Study 400-05-006 in Soft Tissue Bleeding

Primary Endpoint	Associated value and statistical significance for drug (proportions of success within 10 minutes)	Associated value and statistical significance for active control (Surgicel®)
The primary endpoint was haemostatic success, defined as the absence of bleeding at the TBS at 10 minutes following randomisation to treatment.	95.5%	81.2%

Overall the treatment difference (log-rank test) was highly significant ($p<0.001$) in favour of EVICEL.

Clinical Trial in Vascular Surgery (400-05-001)

This was a Phase III, multicentre, prospective, randomised, controlled, parallel group study carried out at centres in the UK and US. The study population comprised patients undergoing vascular procedures utilising uncoated or heparin-coated PTFE prosthetic graft material, with at least one end-to-side anastomosis to a femoral or upper extremity artery.

Table 6. Results of Study 400-05-001 in Vascular Surgery

Primary Endpoint	Associated value and statistical significance for drug (proportions of success within 4 minutes)	Associated value and statistical significance for active control (Manual Compression)
The primary endpoint was haemostatic efficacy, defined as the absence of bleeding at the study anastomotic site (SAS) 4 minutes following randomisation to treatment. The SAS was the final anastomosis to the femoral or upper extremity artery, with the exception of the femoral-femoral procedure when the SAS was the proximal anastomosis performed as the final anastomosis in the procedure.	85.3%	38.9%

Overall the treatment difference (log-rank test) was highly significant ($p<0.001$) in favour of EVICEL.

Clinical Trials in Liver Surgery

Study results for two comparative clinical trials in liver surgery are presented in Tables 7 and 8. The open-label, non-comparative study OFI LIV 002 UK contributes to safety (exposure) data on Crosseal but does not provide a controlled evaluation of efficacy and is thus not presented below.

Table 7. Results of Study Q LIV 008 US in Liver Resection Surgery

Primary Endpoint	Associated value for Crosseal	Associated value for control (standard of care FDA approved topical hemostatic agents)	Statistical significance
The primary efficacy variable was the time to achieve hemostasis, defined as the interval between T_0 and T_1: • T_0: The time of application of a gauze to the surface of the liver after the resection was completed and all the bleeding points had been controlled by suture or cauterization. • T_1: When there is no further evidence of bleeding from the cut surface after direct observation for a period of 1 minute.	5.3 minutes	7.7 minutes	one-sided p = 0.011; two-sided p = 0.021
Occurrence of abdominal collections of fluid	2 patients (3.4%)	9 patients (14.3%)	one-sided p = 0.037 two-sided p = 0.050
The proportion of patients who exhibited one of the following complications: re-operation (for any reason), diagnosis of abdominal collections, bilious aspect of drain fluid for at least one day	10 (17.2%) control	23 (36.5%)	two-sided p = 0.017

The population of patients undergoing living related donor liver graft surgery consisted of two radically different groups. Graft donors were normal healthy adults undergoing a liver resection, whereas graft recipients were seriously ill infants or children undergoing cut-down liver transplantation. The two groups were therefore analysed separately for

most of the study parameters. No significant differences were found in any of the parameters evaluated, with the exception of the assessment of quality of haemostasis, as shown in Table 8.

Table 8. Results of Study Q LIV 003 US in Living, Related Donor Liver Graft Transplantation

Endpoint	Associated value for Crosseal	Associated value for control (Tissucol Fibrin Sealant Kit)	Statistical significance
Quality of hemostasis 10 minutes after application in graft donor and 10 minutes after reperfusion in graft recipient	17 patients: no bleeding	11 patients: no bleeding 6 patients: adequate hemostasis	p=0.009

Clinical Trials in Orthopaedic Surgery

Study results for two comparative clinical trials in orthopaedic surgery are presented in Tables 9 and 10. Study OFI TKR 004 US is incomplete and study OFI THR 005 UK was a dose-finding pilot study. These studies contribute to safety (exposure) data on Crosseal but do not provide a controlled evaluation of efficacy and are thus not presented below.

Table 9. Results of Study Q THR 009 US in Total Hip Replacement Surgery

Endpoint	Associated value for Crosseal	Associated value for control (standard surgical technique)	Statistical significance
Reduction in total peri-operative blood loss	Adjusted (geometric) mean blood loss = 626 mL:	Adjusted (geometric) mean blood loss = 819 mL	Reduction of 197mL; one-sided p = 0.0071, two-sided p = 0.0141

Table 10. Results of Study OFI TKR 001 IL in Total Knee Replacement Surgery

Endpoint	Associated value for Crosseal	Associated value for control (standard surgical technique)	Statistical significance
Mean post-operative blood loss via drain	383±295 mL	885±408 mL	p< 0.001
Number of patients requiring blood or blood product transfusion:	6	19	p< 0.001

Clinical Trial in Neurosurgery

This was a Phase III, multicentre, randomised, controlled study carried out at centres in the EU. The study population comprised of patients undergoing elective posterior fossa or supratentorial procedure. Upon completion of the primary suture dural repair, the closure was evaluated for intra-operative cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver 20-25cm H_2O for 5-10 seconds. If a CSF leak was identified, patients were to be enrolled into the study and randomised to either EVICEL or to adjunctive dural closure techniques using additional repair sutures only (control) in a 2:1 allocation ratio.

Table 11 Study 400-09-001 Results for Primary Efficacy Endpoint (FAS)

Endpoint	EVICEL	Control	Treatment Difference	p-value†
Proportion of successes* (intra-operative watertight closure) in the treatment of intra-operative CSF leakage. **Success was defined as no CSF leakage from dural repair intra-operatively, during Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.*	82/89 (92.1%)	19/50 (38.0%)	54.1% (95% CI: 38.9, 67.4)	<0.001

† Fisher's exact and Chi-squared test

DETAILED PHARMACOLOGY

Thrombin is a highly specific protease that transforms the fibrinogen contained in Human Clottable Protein into fibrin. Thrombin is partly adsorbed by the fibrin so formed. Excess thrombin, if any, is inactivated by protease inhibitors in the blood.

Pharmacology studies conducted with EVICEL have focused on evaluating the haemostatic efficacy, physical properties and the stability of the clot once formed, in comparison with QUIXIL and other marketed fibrin sealants (Tissucol™ and Tisseel™). These pharmacological studies with EVICEL indicate that the haemostatic efficacy and *in vivo* clot stability of EVICEL are at least as good as those of QUIXIL.

The haemostatic properties demonstrated by EVICEL and QUIXIL in both studies using the rat kidney haemorrhage model were similar. EVICEL clot longevity, in the rat abdominal wall incision model, was shown to be comparable to that of QUIXIL and is similar to that of other marketed fibrin sealants such as Tissucol™ and Tisseel™ indicating that the removal of endogenous plasminogen from EVICEL compensates for the lack of the fibrinolysis inhibitor present in the other fibrin sealants.

In conclusion, the findings of pharmacological studies are consistent with the use of EVICEL as supportive treatment in surgery where standard surgical techniques are

insufficient, for improvement of haemostasis, and to promote sealing, or as suture support for haemostasis in vascular surgery.

TOXICOLOGY

The toxicological assessment of EVICEL and its major components, Human Fibrinogen and Human Thrombin, was based primarily on the data showing comparability of QUIXIL and EVICEL, safety data gathered for QUIXIL including toxicology of the individual substances present in the final formulation that are not derived from pooled human plasma, as well as local tolerance testing of the combined fibrin sealant components. The safety (toxicity) of fibrinogen, thrombin and the final formulation was not studied extensively in animals due to the fact that the components of the product are human in origin, and stimulation of the immune system would be expected. Such an immune activation may confound interpretation of results of toxicology studies, possibly mimicking or masking actual toxicological effects.

The systemic toxicity and/or local tolerance, as well as haemostatic efficacy, of EVICEL were evaluated in a rabbit study using a standardized rabbit partial hepatectomy model. Previously, this model had been used to assess QUIXIL along with studies in rats, using a partial pancreatic resection model or tolerance in various wounded tissues. These studies demonstrated the absence of major macroscopic signs of local intolerance or systemic toxicity in the presence of haemostatic efficacy. In addition, mutagenicity studies demonstrated that Human Thrombin and Human Fibrinogen are non mutagenic. In a study that tested the ocular tolerance, QUIXIL was found to be slightly irritating to the eye.

Although studies with QUIXIL showed no evidence of local intolerance or systemic toxicity, the tranexamic acid component was shown to have a neurotoxic effect in a rabbit model. However, EVICEL is formulated without tranexamic acid. Safety of EVICEL was also shown following subdural administration in the rabbit with follow up on local tissue response.

Of the other ingredients or residues the toxicology of TnBP and Triton X-100, and the excipients human albumin and mannitol were examined. Studies evaluating TnBP and Triton X-100 showed that residual levels of these substances in EVICEL are far below the cytotoxic dose: for both and Fibrinogen and Thrombin TnBP$\leq$5 and Triton X-100<5.

Human albumin is added to the Thrombin component of EVICEL as a stabilizer, to a concentration of 5.0-6.5 mg/mL. In animals, single dose toxicity testing of Human Albumin is of little relevance and does not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated dose toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models. To date, Human Albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential. No signs of acute toxicity have been described in animal models (CPMP/PhVWP/BPWG/2231/99 rev.2, core SPC for human albumin, CHMP, 2005).

Mannitol is added to the Thrombin component of EVICEL to a concentration of 18.5-20.5 mg/mL. There are no inherent safety concerns with mannitol (mannite,1,2,3,4,5,6-hexanehexol, CAS No: 69-65-8, EC(EINECS) No: 200-711-8) for its use as an excipient. The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions may occur when mannitol is used as an excipient.

REFERENCES

1) Levy O, Martinowitz U, Oran A, Tauber H, Horoszowski H. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. *J Bone Joint Surg.* 1999; 81-A(11): 1580-1588.

2) Wang GJ, Hungerford P, Savory C, Rosenberg A, Mont M, Burks S, Mayers L, Spotnitz W. Use of fibrin sealant to reduce bloody drainage and hemoglobin loss after total knee arthroplasty. *J. Bone and Joint Surg*. 2001; 83-A (10):1503-1505.

3) Crawford R, Giangrande P, Murray D. Fibrin sealant reduces blood loss in total hip arthroplasty. *Hip International.* 1999; 9(3): 127-132.

4) Nur I, Routledge G, Lushkov G, Paulmier P, Virat M. Absorption and elimination of α- thrombin and tranexamic acid after fibrin sealant application on resected livers in rabbits. *Blood Coagulation and Fibrinolysis*. 1998; 9(6): 533-537.

5) Green AL, Arnaud A, Batiller J, Eljamel S, Gauld J, Jones P, Martin D, Mehdorn M, Ohman J, Weyns F. A multicentre, prospective, randomized, controlled study to evaluate the use of a fibrin sealant as an adjunct to sutured dural repair. *Br J Neurosurgery* 2014; Aug 12: 1-7.

PART III: CONSUMER INFORMATION

EVICEL

Fibrin Sealant Kit

This leaflet is part III of a three-part "Product Monograph" published when the drug is approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about EVICEL. Contact your doctor or pharmacist if you have any question about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

EVICEL is used as supportive treatment to reduce bleeding and oozing during and after the operation. Evidence of efficacy and safety has been demonstrated in the following clinical trials (1) Liver surgery such as liver resection and reduced-size liver transplantation (2) Orthopedic surgery such as total hip replacement and total knee replacement, (3) Retroperitoneal/intra-abdominal surgery, (4) Vascular surgery.

In addition, EVICEL is used to support watertight closure of the cerebral envelopes (dura mater) during neurosurgery when other surgical techniques are insufficient. (See Use in Neurosurgery)

What it does:

Fibrinogen is a concentrate of clottable protein and thrombin is an enzyme that causes clottable protein to coalesce. Thus, when the two components are mixed together they clot instantly.

When it should not be used:

Do not use EVICEL:

- If you are hypersensitive (allergic) to products made from human blood or to any of the other ingredients of EVICEL. Signs of such reactions include hives, rash, tightness of the chest, wheezing, drop in blood pressure and breathing difficulties. If these symptoms occur, the administration has to be discontinued immediately.
- For treatment of severe or brisk arterial bleeding

The spray application of EVICEL should not be used in endoscopic (intra luminal) procedures. For laparoscopy, see sections Warnings and Precautions, and Proper Use of This Medication.

What the medicinal ingredient is:

This product is a human fibrin sealant kit, which is supplied as a package containing two components called Human Clottable Protein and Thrombin.

What the non-medicinal ingredients are:

Human Clottable Protein contains the following non-medicinal ingredients:	Thrombin contains the following non-medicinal ingredients:
Arginine hydrochloride	Calcium chloride
Calcium chloride	Human albumin
Glycine	Mannitol
Sodium chloride	Sodium acetate
Sodium citrate	Water for injection
Water for injection	

What dosage forms it comes from:

The EVICEL kit is available as 2x1 mL, 2x2 mL or 2x5 mL kits each containing one vial of Human Clottable Protein and one vial of Thrombin as frozen, sterile solutions, which is white to slightly yellowish opaque frozen mass. The thawed preparation is clear and colourless to slightly yellowish.

Human Clottable Protein contains 50-90 mg/mL clottable proteins. Thrombin contains 800-1200 IU/mL human thrombin.

WARNINGS AND PRECAUTIONS

WARNING

For topical use only. Do not apply intravascularly.

When medicinal products prepared from human blood or plasma are given to patients, the risk of transmission of an infection cannot be totally ruled out.

Life-threatening/fatal air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer fibrin sealants including 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. To reduce the risk of potentially life threatening air embolism EVICEL should be sprayed using pressurized CO_2 gas only.

Before you use EVICEL, talk to your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Data are too limited to support the safety and effectiveness of EVICEL in children.

There is not enough information available to know whether any particular risks are associated with the use of EVICEL during pregnancy, during labor and delivery or whilst breast-feeding. However, since

EVICEL is used during a surgical operation, if you are pregnant or breast-feeding you should discuss the overall risks of the operation with your doctor.

When spraying EVICEL, your doctor may monitor changes in blood pressure, pulse, oxygen saturation and end tidal carbon dioxide because of the possibility of occurrence of air or gas embolism.

Use in Tissue Gluing, Endoscopy or Gastro-Intestinal Anastomoses

Adequate data are not available to support the use of this product in tissue gluing, application through an endoscope for treatment of bleeding or in gastro-intestinal anastomoses.

Use in Neurosurgery

The use of EVICEL has not been studied in the following procedures, and there is therefore no information to show that it would be effective in these procedures:

- Gluing tissues together or fixing dural patches or implants
- Surgery to the brain except for support of watertight closure of cerebral envelopes (dura mater)
- Sealing in transphenoidal (through the nose) and otoneurosurgical (through the ear) procedures
- It is not known whether radiation therapy within a week after surgery could affect the effectiveness of fibrin sealant when used for suture line sealing during neurosurgery.

INTERACTIONS WITH THIS MEDICATION

No formal interaction studies have been performed. Similar to comparable products or thrombin solutions, the product may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.

PROPER USE OF THIS MEDICATION

Usual Dose: The doctor treating you will administer EVICEL during surgery.

During your operation, your doctor will drip or spray EVICEL onto raw tissue during operations, using an application device. This device allows equal amounts of the two components of EVICEL to be administered at the same time, and ensures that they mix evenly, which is important for the sealant to have its optimal effect. Your doctor will follow the spray distance and pressure recommended by the manufacturer in the spray application of EVICEL (see Table from Method of Application by Spraying).

The amount of EVICEL that will be applied depends on the surface area of tissue to be treated during the operation. It will be dripped onto the tissue in short bursts or sprayed in very small amounts (0.1-

0.2 mL), to produce a thin, even layer. If application of a single layer of EVICEL does not completely stop the bleeding, a second layer may be applied.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, EVICEL can have side effects, although not everybody gets them.

EVICEL is a fibrin sealant. Fibrin sealants in general may, in rare cases (1 to 10 patients in 10,000), cause an allergic reaction. If you experience an allergic reaction you might have one or more of the following symptoms: skin rash, hives or wheals (nettle-rash), tightness of the chest, chills, flushing, headache, low blood pressure, lethargy, nausea, restlessness, increased heart rate, tingling, vomiting or wheezing. No allergic reactions have so far been reported in patients treated with EVICEL.

There is also a theoretical possibility that you could develop antibodies to the proteins in EVICEL, which could potentially interfere with blood clotting.

In clinical studies with EVICEL some undesired events occurred for which a causal relation to the application of EVICEL could not be excluded. After abdominal surgery some patients presented with an abscess, and in vascular surgery some cases of an occluded graft occurred which had do be re-operated. Some undesired effects reported in the neurosurgery clinical trial included meningitis, blood accumulation and accumulation of CSF fluid in the brain cavities.

If you feel unwell tell your doctor immediately, even if your symptoms are different from those just described.

If you notice any other side effects, please inform your doctor or pharmacist.

HOW TO STORE IT

Store frozen at ≤ -18°C. Do not use EVICEL after the expiry date printed on the carton.

Vials must be stored in an upright position in their carton and protected from light.

If thawed, do not refreeze. After thawing, the thaw date should be noted on the carton. Thawed, unopened vials can be stored at:

- 2- 8°C for up to 30 days, or
- up to 24 hours at room temperature in their carton

The thawed product should be used within 30 days from the thaw date or the product expiry date, whichever comes first.

Once drawn up into the application device, they must be used immediately.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free telephone: 866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to: 866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa ON K1A 0K9

    Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: *Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.omrix.com or by contacting Ethicon Customer Support Center at (800) 268-5577.

Manufactured by:
Omrix Biopharmaceuticals Ltd
MDA Blood Bank,
Sheba Hospital, Ramat-Gan
POB 888, Kiryat Ono 5510801
ISRAEL

Imported into Canada and distributed by:
Johnson & Johnson Medical Products,
a division of Johnson & Johnson Inc.,
Markham, Ontario L3R 0T5
CANADA

This leaflet was prepared by Omrix Biopharmaceuticals Ltd.

Last revised: October 13, 2017