

The format of this leaflet has been determined by the Ministry of Health and the content thereof has been checked and approved.

Physician's Leaflet

EVICEL®

Human Surgical Sealant

1. Name of the Medicinal Product

EVICEL® Human Surgical Sealant

2. Qualitative and Quantitative Composition

The active ingredients are as follows:

	1 ml of Solution	2 ml of Solution	5 ml of Solution
Component 1 (BAC2) Human clottable protein containing mainly fibrinogen and fibronectin*	50 – 90 mg	100 – 180 mg	250 – 450 mg
Component 2 (Thrombin) Human Thrombin	800 – 1,200 IU	1,600 – 2,400 IU	4,000 – 6,000 IU
Calcium Chloride	5.6 – 6.2 mg	11.2 – 12.4 mg	28 – 31 mg

* Total quantity of protein is 80 – 120 mg/ml.

For a full list of excipients see Section 6.1.

3. Pharmaceutical Form

Solutions for sealant.

Clear and colourless to slightly yellowish solutions.

4. Clinical Particulars

4.1. Therapeutic Indications

General haemostasis: EVICEL® is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.

Efficacy has been demonstrated in liver surgery and orthopaedic surgery (see Section 5.1).

EVICEL® is also indicated as suture support for haemostasis for suture line sealing in dura mater closure.

4.2. Posology and Method of Administration

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

4.2.1. Posology

The volume of EVICEL® to be applied and the frequency of application should always be oriented toward 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 8 ml 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 trauma) 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.

EVICEL® should be dripped or sprayed onto the tissue in short bursts (0.1 – 0.2 ml) to produce a thin, even layer.

The maximum recommended dosage of combined product is 20 ml for adults, 10 ml for children and 5 ml for infants.

In orthopaedic surgery, there are insufficient data available to recommend the use of EVICEL® in patients of less than 18 years of age.

4.2.2. Method of Administration

For epilepsial use.

To mitigate the risk of potentially life-threatening air embolism, EVICEL® should be sprayed using pressurised CO₂ gas only.

Prior to applying EVICEL®, the surface area of the wound should be dried by standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices).

The product should only be reconstituted and administered according to the instructions and with the devices recommended for this product.

See Sections 4.4 and 6.6 for specific spray recommendations on the required pressure and distance from tissue per surgical procedure and length of application tip.

4.3. Contraindications

- EVICEL® must not be applied intravascularly.
- Hypersensitivity to the active substances or any of the excipients listed in Section 6.1.
- Spray application of EVICEL® should not be used in endoscopic procedures. For laparoscopy, see Section 4.4.
- EVICEL® must not be used for sealing the suture line in dura mater if there are gaps of greater than 2 mm after suturing.
- EVICEL® must not be used as a glue for the fixation of dural patches.
- EVICEL® must not be used as a sealant when the dura mater cannot be sutured.

4.4. Special Warnings and Precautions for Use

- For epilepsial use only. Do not apply intravascularly.
- Life-threatening thromboembolic complications may occur if the product is unintentionally applied intravascularly.
- 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 indicated pressures and/or in close proximity to the tissue surface.
- In order to mitigate the risk of air or gas embolism:
 - EVICEL® should be sprayed using pressurised CO₂ gas only.
 - EVICEL® spray application should only be used if it is possible to accurately judge the spray distance, especially during laparoscopy. Spray distance from tissue and pressure should be within the ranges indicated by the manufacturer (see table in Section 6.6 for pressures and distances).
 - When spraying EVICEL®, changes in blood pressure, pulse, oxygen saturation and end-tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism.
 - When using accessory tips with this product, the instructions for use of the tips should be followed.
- EVICEL® should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.
- 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 gastrointestinal anastomoses.
- The concomitant use of EVICEL® for dural suture line sealing with implants from synthetic materials or dural patches has not been evaluated in clinical studies.
- The use of EVICEL® in patients undergoing radiotherapy within 7 days after surgery has not been evaluated. It is not known whether radiation therapy could affect the efficacy of fibrin sealant when used for suture line sealing in dura mater closure.
- Complete haemostasis should be achieved before application of EVICEL® to seal the dural suture line.
- The use of EVICEL® as a sealant in transphenoidal and otoneurosurgical procedures has not been studied.
- 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.
- As with any protein product, allergic-type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately.
- 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 infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. 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 that EVICEL® is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5. Interaction with Other Medicinal Products and Other Forms of Interaction

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.

4.6. Pregnancy and Lactation

The safety of fibrin sealants/haemostatics for use in human pregnancy 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.

4.7. Effects on Ability to Drive and Use Machines

Not relevant.

4.8. Undesirable Effects

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.

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 indicated pressures and/or in close proximity to the tissue surface.

Hypersensitive 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 antihistamines. 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 (DIC), and there is also a risk of anaphylactic reaction (see 4.4).

For safety with respect to transmissible agents, see Section 4.4.

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

MedDRA System Organ Class	Preferred Term
<i>Adverse Reactions in Retroperitoneal or Intra-abdominal Surgery Study</i>	
Infections and infestations	Abdominal abscess
<i>Adverse Reactions in Vascular Surgery Study</i>	
Infections and infestations	Graft infection, staphylococcal infection
Vascular disorders	Haematoma
General disorders and administration site conditions	Oedema peripheral
Investigations	Decreased haemoglobin
Injury, poisoning and procedural complications	Incision site haemorrhage Vascular graft occlusion Wound Post-procedural haematoma Post-operative wound complication
<i>Adverse Reactions in Neurosurgery Study</i>	
Infections and infestations	Meningitis
Nervous system disorders	Intracranial hypotension (CSF leakage) CSF rhinorrhoea Headache Hydrocephalus Subdural hygroma
Vascular disorders	Haematoma

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.

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 that were considered to be possibly related to the study product. These included intracranial hypotension (CSF leakage), CSF rhinorrhoea, 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 4/89 (4.5%) subjects treated with EVICEL® (two cases of CSF leakage with impaired wound healing and two cases of rhinorrhoea) and in 1/50 (2.0%) subjects treated with additional sutures.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@MOH.HEALTH.GOV.IL).

Additionally, you may also report to the MAH, Omrix Biopharmaceuticals Ltd. by one of the following 2 ways:

Call Omrix switchboard: 03-5316531

Email: ra-omrilpv@its.jnj.com

4.9. Overdose

No case of overdose has been reported.

5. Pharmacological Properties

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: local haemostatics, ATC code: B02BC30 combinations.
The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin 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 crosslinking of fibrin. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.
Clinical studies demonstrating haemostasis and suture support were conducted in a total of 147 patients (75 with EVICEL®, 72 with control) undergoing vascular surgery with PTFE grafts and in a total of 135 patients (66 with EVICEL®, 69 with control) undergoing retroperitoneal and intra-abdominal surgery.
The efficacy of EVICEL® for suture line sealing in dura mater closure was demonstrated in 139 patients (89 treated with EVICEL® and 50 controls) undergoing craniotomy/craniectomy procedures.
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.

5.2. Pharmacokinetic Properties

EVICEL® is intended for epislesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.
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 ¹²⁵I-thrombin it was shown that a slow absorption of biologically inactive peptides resulting from the breakdown of thrombin occurred, reaching a C_{max} in the plasma after 6 – 8 hours. At the C_{max}, the plasma concentration represented only 1 – 2% of the applied dose.
Fibrin sealants/haemostatics are metabolised in the same way as endogenous fibrin, by fibrinolysis and phagocytosis.

5.3. Pre-clinical Safety Data

Studies performed in bacteria to determine mutagenicity were negative for thrombin alone, Biological Active Component (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.
After local application, absorption of thrombin into the plasma is slow and consists principally of thrombin degradation products which are eliminated.
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 5 µg/ml.
Neurotoxicity studies performed with EVICEL® confirmed that subdural administration in the rabbit was not associated with any evidence of neurotoxicity. Neurobehavioral observations for 14±1 days showed no abnormal findings. No major macroscopic signs of local intolerance and no treatment-related macroscopic findings were observed. Analysis of cerebrospinal fluid did not reveal major signs of inflammation.

6. Pharmaceutical Particulars

6.1. List of Excipients

<i>Excipients fibrinogen solution</i>	<i>Excipients thrombin solution</i>
Arginine Hydrochloride	Human Albumin
Glycine	Mannitol
Sodium Chloride	Sodium Acetate
Sodium Citrate	Water for Injections
Calcium Chloride	
Water for Injections	
Each ml contains 11.6 – 12.9 mg sodium.	

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products and should always be applied with the device supplied.

6.3. Shelf Life

The approved shelf life of EVICEL® is 24 months storage at ≤ -18°C.
After thawing, unopened vials can be stored at 2 – 8°C and protected from light, for up to 30 days.

6.4. Special Precautions for Storage

The vials must be stored in an upright position.
Store in a freezer at or below -18°C. Keep the vials in the outer carton in order to protect from light. Do not refreeze.
After thawing, unopened vials can be stored at 2 – 8°C and protected from light for up to 30 days, without being frozen again during this period. At the end of this period the product has to be used or discarded.

6.5. Nature and Contents of the Container

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 of solution of Human Fibrinogen and Human Thrombin respectively.
An application device and appropriate accessory tips are supplied separately.

6.6. Special Precautions for Disposal and Other Handling

• Thawing:

The vials should be thawed 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
37°C (e.g., water bath, using aseptic technique, or by warming vials in the hand): vials should be thawed 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 37°C.

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

• Preparation (see Figure 1)

The solution should be clear and colourless to slightly yellowish. Do not use solutions that are cloudy or have deposits.
EVICEL® should only be applied using the CE-marked EVICEL® Application Device and optional use of accessory tips to the device. Detailed instructions for use of EVICEL® in conjunction with the application device and optional accessory tips are provided with the application device and of the accessory tips.
The accessory tips should only be used by qualified persons adequately trained in laparoscopic, laparoscopic-assisted or open surgical procedures.
The application device package contains a specially designed device for applying the product and a tube with 0.2 µm bacteriological filter which is used to supply pressurised gas to the device to aerosolise EVICEL® when applied by spraying. The application devices are sterile as long as the package is unopened and undamaged, and must only be used once. No needles are involved in the preparation of EVICEL® for administration.
Draw the contents of the two vials into the administration device, following the instructions in Figure 1.
Both syringes should be filled with equal volumes, and should not contain air bubbles.

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

• Spray Application

Connect the short tube on the application device to the male luer-lock end of the long gas tube. Connect the female luer-lock of the gas tube (with the 0.2 µm bacteriostatic filter) to a pressure regulator. The pressure regulator should be used in accordance with the manufacturer's instructions.
To mitigate the risk of life-threatening air embolism, EVICEL® should only be sprayed using pressurised CO₂ (see table below).
When applying EVICEL® using a spray device, be sure to use pressures and distances from the tissue within the ranges indicated by the manufacturer:

Surgery	Spray Set to Be Used	Applicator Tips to Be Used	Pressure Regulator to Be Used	Distance from Target Tissue	Spray Pressure
Open surgery	EVICEL® Applicator Device	6 cm Yellow Flexible Tip	Omrix Pressure Regulator	10 – 15 cm / 4 – 6 inches	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 inches	15 – 20 psi / 1.0 – 1.4 bar
		45 cm Yellow Flexible Tip		4 – 10 cm / 1.6 – 4 inches	20 psi / 1.4 bar

The product should 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.
When spraying EVICEL®, changes in blood pressure, pulse, oxygen saturation and end-tidal CO₂ should be monitored because of the possibility of occurrence of air or gas embolism.
When using accessory tips with this product, the instructions for use provided with the tips should be followed.

• Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Manufactured by:



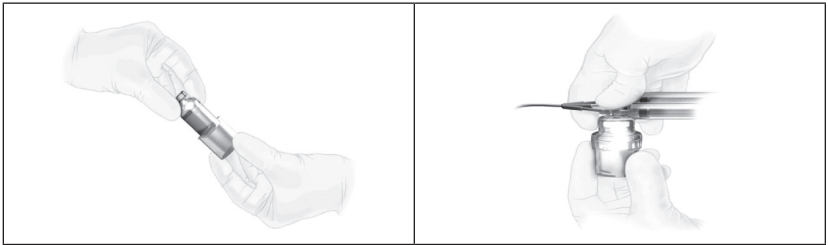
Omrix Biopharmaceuticals Ltd.
MDA Blood Bank, Sheba Hospital
POB 888, Kiryat Ono 5510801, ISRAEL

8. Date of Revision of the Text

February 2015

Figure 1. Instructions for Use of the Administration Device

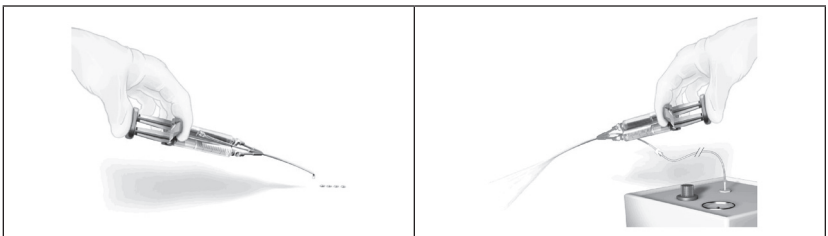
Holding the syringe barrels with one hand, loosen the syringe pistons by sliding them back and forth.



1. Insert the two vials (BAC2 and Thrombin) into the two sterile vial cups. The vial cups must be handled using sterile technique.
2. Holding the vial cup, press the top of the vial into the vial connector which is attached to the applicator (as shown). Repeat with the second vial.



3. Holding the syringe barrels with one hand, aspirate both syringes slowly (vials facing up). If needed, inject back into vial and aspirate again to expel air.
4. While holding the syringe barrels with one hand, gently turn the vial connector anti-clockwise with the other hand. The vial connector/vial/vial cup combination disconnects automatically.



5. If spraying is required, connect the tubing to the pressure regulator. The applicator is now ready for use.