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 excipients see section 6.1.

3. Pharmaceutical Form

Solutions for sealant.

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 5.1).

4.2. Posology and Method of Administration

The use of EVICEL® is restricted to experienced surgeons

4.2.1. Posology

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, dosages have typically ranged from 5 to 10 ml of the combined product. For some procedures (e.g. liver traumata, or the sealing of large burned surfaces) 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 and Route of Administration

For epilesional use.

Prepare the solutions as described in Section 6.6. Before application, the surface of the wound should be as dry as possible. See 6.6 for more detailed instructions.

4.3. Contra-indications

- EVICEL® must not be applied intravascularly.
- Hypersensitivity to the active substances or any of the excipients.

4.4. Special Warnings and Precautions for Use

- For epilesional use only. Do not apply intravascularly.
- Adequate data are not available to support the use of this product in tissue glueing, application through an endoscope for treatment of bleeding or in gastrointestinal anastomoses.
- Life threatening thromboembolic complications may occur if the product is unintentionally applied intravascularly.
- Air or gas embolism has occurred with the use of spray devices employing pressure regulators to administer EVICEL®. This event appears to be related to the use of the spray device at higher than recommended pressures and in close proximity to the surface of the tissue. When applying EVICEL® using a spray device, be sure to use the pressure within the pressure range recommended by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 1.4-1.7 bars. Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying EVICEL®, 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.
- 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 has to 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 infections 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, HCV and HBV.

The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoeisis (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 Medicaments 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

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.

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

Inadvertent intravascular injection could lead to thromboembolic event and DIC, and there is also a risk of anaphylactic reaction (see 4.4).

A post marketing fatality was reported in association with the use of EVICEL® when applied using a spray device. The case involved an attempt to stop active bleeding by applying EVICEL® using a spray device attached to a wall unit at a higher than recommended pressure for the spray device. In addition, the spray head was placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant. The patient suffered a fatal air embolism.

For safety with respect to transmissible agents, see 4.4.

As with any plasma derivative, anaphylactic reactions may occur in rare cases. No adverse events of this type were reported during the conduct of the clinical trials.

Mild reactions can be managed with anti-histamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

4.9. Overdose

No case of overdose has been reported.

5. Pharmacological Properties

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: local haemostatics, ATC code: B02BC

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 form Factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both the conversion of fibrinogen and the crosslinkage 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 sealing were conducted in liver surgery (liver resection and liver transplantation) and orthopaedic surgery (total hip replacement and total knee replacement surgery). In addition a Phase II study has been performed in vascular surgery (carotid endarterectomy). Study designs and patient numbers are summarised in the following table:

Surgical Procedure	**Study Design and Phase**	**Number of Patients**
Liver resection	Phase III; Single-blind, randomised, standard-treatment active controlled, parallel-group, multicentre study.	Total 121; Quixil* group: 58 Control group: 63
Living related donor liver transplantation	Phase II; Open label, active controlled, non-randomised, comparative clinical study.	Total 34; Quixil* group: 17 Control group: 17
Liver resection and reduced size liver transplantation	Phase II; Open, non comparative, prospective study.	21 patients, all treated with Quixil*
Total Hip Replacement	Phase III; Single-blind, randomised, controlled, multicenter study.	Total 97; Quixil* group: 54 Control group: 43
Total Knee Replacement	Phase III; Single-blind randomised controlled multicentre study.	Total: 59; Quixil* group: 29 Control group: 30
Total Knee Replacement	Phase III; Single blind, randomised, parallel group, standard treatment control multicentre study.	Total: 53; Quixil* group:25 Control group: 28
Total Hip Replacement	Phase II; Open pilot study comparing three regimens of administration of Quixil in THR with matched historical controls.	13 patients, all treated with Quixil*
Carotid Endarterectomy with PTFE graft	Phase II; Single blind, prospective, randomized, active controlled pilot study.	Total: 20 Quixil* group: 10 Control group: 10

* First generation of Human Surgical Sealant

The clinical trials in liver surgery included eight paediatric patients of which five were less than 2 years old. In one study involving 59 patients undergoing total knee replacement surgery, Quixil (first generation of Human Surgical Sealant) was shown to be haemostatically effective in patients treated with Low Molecular Weight Heparin prior to surgery.

5.2. Pharmacokinetic Properties

EVICEL® is intended for epilesional 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 ^{125}I-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

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

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.

6. Pharmaceutical Particulars

6.1. List of Excipients

BAC2:
Arginine Hydrochloride
Glycine
Sodium Chloride
Sodium Citrate
Calcium Chloride
Water for Injections

Thrombin Solution:
Human Albumin
Mannitol
Sodium Acetate
Water for Injections

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

2 years.

6.4. Special Precautions for Storage

The vials must be stored in an upright position. Store at ≤ -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.

When BAC2 and Thrombin have been drawn up into the administration device they must be used immediately.

6.5. Nature and Contents of the Container

EVICEL® consists of 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 (BAC2 and Thrombin respectively), and an application device package.

The CE-marked application device package contains a sterile, single-use, disposable two-syringe device arranged in clear PVC tray, which is sealed with Tyvek peel paper. The sealed tray is contained in a sealed pouch constructed of paper/polyethylene and supplied in a cardboard carton.

6.6 Instructions for Use, Handling and Disposal

- **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

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.

- **Preparation (see Figure 1)**

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. 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.

- **Spray Application**

EVICEL® can be sprayed using pressurized CO_2 or compressed air.

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 bacteriostatic filter) to a pressure regulator capable of delivering 1 to 2 bars pressure. The pressure regulator should be used in accordance with the manufacturer's instructions. Utilize spray pressure that is within the recommended guidelines by the device manufacturer [e.g. a pressure of 1.4 to 1.7 bars (measured by gas flow)]..

Ensure that distance between the spray head and the application bed is within the recommended guidelines by the device manufacturer. The distance between the nozzle and the tissue surface should ideally be 10 to 15 cm. 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.

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

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

7. Manufactured by:

Omrix Biopharmaceuticals Ltd. (+logo)
MDA Blood Bank, Sheba Hospital, Ramat Gan
POB 888, Kiryat Ono, 55000, ISRAEL

8. Date of Revision of the Text

February 2013

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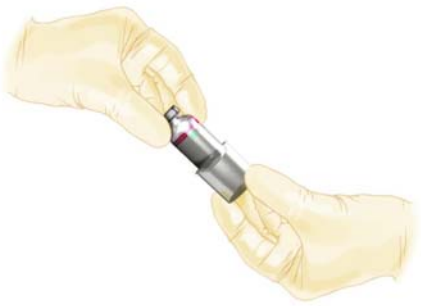
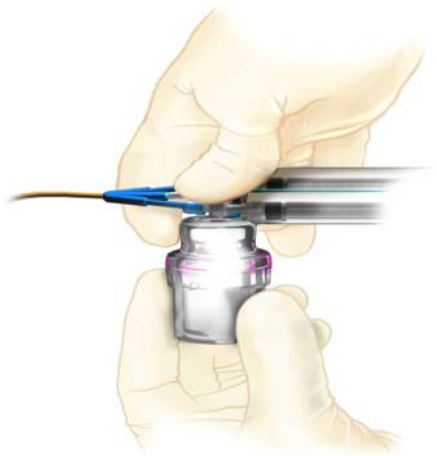
Figure 1. Instructions for Use of the Administration Device

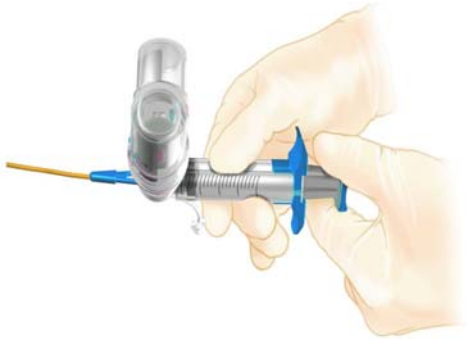
Holding the syringe barrels with one hand, loosen the syringe pistons by sliding them back and forth.



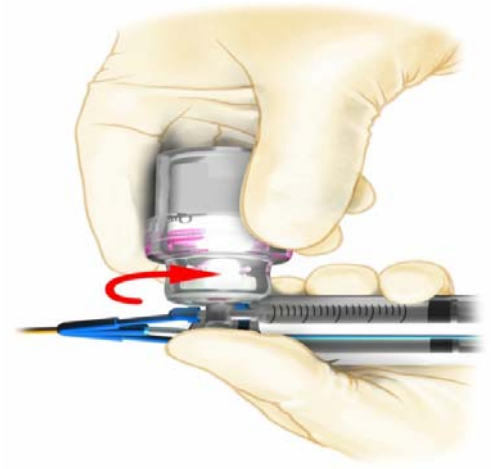
1. Insert the two vials (BAC2 and Thrombin) into the two sterile vial cups. The vial cups must be handled using sterile technique.



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 syring 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.