Product Information as approved by the CHMP on 15 November 2012, pending endorsement by the European Commission

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EVICEL solutions for sealant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredients are as follows:

	1 ml vial	**2 ml vial**	**5 ml vial**
Component 1 Human clottable protein containing mainly fibrinogen and fibronectin *	50 – 90 mg	100 – 180 mg	250 – 450 mg
Component 2 Human thrombin	800 – 1,200 IU	1,600 – 2,400 IU	4,000 – 6,000 IU

* 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 or slightly opalescent solutions.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EVICEL is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis (see Section 5.1).

EVICEL is also indicated as suture support for haemostasis in vascular surgery.

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

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 in vascular surgery, the individual dosage used was up to 4 ml, 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.

Method and route of administration

For epilesional use.

To avoid the risk of potentially life threatening air embolism EVICEL should be sprayed using pressurised CO_2 gas only.

Prior to applying EVICEL the surface area of the wound needs to 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 to any of the excipients.

Spray application of EVICEL should not be used in endoscopic procedures. For laparoscopy, see Section 4.4.

4.4 Special warnings and precautions for use

For epilesional 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 pressure regulator to administer EVICEL.EVICEL should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer EVICEL. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.

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 recommended by the manufacturer (see table in Section 6.6 for pressure and distance).

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.

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, neurosurgery, application through an endoscope for treatment of bleeding or in gastrointestinal anastomoses.

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 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.

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 erythropoyesis (e.g. haemolytic anaemia).

It is strongly recommended that every time 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.

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

Life threatening air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer EVICEL. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.

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**
Adverse Reactions in Retroperitoneal or Intra-Abdominal Surgery Study	
Infections and infestations	Abdominal abscess
Adverse Reactions in Vascular Surgery Study	
Infections and infestations	Graft infection, Staphylococcal infection
Vascular disorders	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

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.

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 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.

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 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 Preclinical 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 mutageneicity, 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

*Human fibrinogen vial***:**
Arginine hydrochloride
Glycine
Sodium chloride
Sodium citrate
Calcium chloride
Water for injections

Human thrombin vial:
Calcium chloride
Human albumin
Mannitol
Sodium acetate
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.

6.3 Shelf life

The approved shelf life of EVICEL is 16 months storage at ≤ -18°C.
After thawing, unopened vials can be stored at 2 - 8°C and protected from light, for up to 25 days. The Fibrinogen and Thrombin components are stable at room temperature for up to 24 hours.

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 25 days, without being frozen again during this period. The new expiry date at 2-8°C should be noted on the carton. At the end of this period the product has to be used or discarded.

The Fibrinogen and Thrombin components are stable at room temperature for up to 24 hours but once drawn up into the application device, they must be used immediately.

6.5 Nature and contents of 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 solution of Human Fibrinogen and Human Thrombin, respectively.

An application device and appropriate accessory tips are supplied separately.

Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

The instructions for use are also described in the healthcare professionals package leaflet part.

- **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 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 37ºC.

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

- **Preparation**

The solutions are clear or slightly opalescent. 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 a tip accessory to the device. Leaflets giving detailed instructions for use of EVICEL in conjunction with the application device and optional accessory are provided with the package of the application device and of the accessory. The accessory tips should only be used by persons adequately trained in laparoscopic, laparoscopic assisted or open surgical procedures.

Draw the contents of the two vials into the application device, following the instructions for use in the device package. Both syringes should be filled with equal volumes, and should not contain air bubbles. No needles are involved in the preparation of EVICEL for administration.

- **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**

To avoid the risk of life-threatening air embolism EVICEL should only be sprayed using pressurised CO_2 (see table below).

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.

When applying EVICEL using a spray device, be sure to use a pressure and a distance from the tissue within the ranges recommended by the manufacturer:

Surgery	**Spray set to be used**	**Applicator tips to be used**	**Pressure regulator to be used**	**Recommended distance from target tissue**	**Recommended spray pressure**
Open surgery	EVICEL Applicator Device	6 cm Yellow Flexible Tip 35 cm Black Rigid Tip	Omrix Pressure Regulator	10-15 cm (4 – 6 inches)	20-25 psi/ 1.4-1.7 bar
Laparoscopic procedures		35 cm Black Rigid Tip		4 – 10 cm (1.6 – 4 inches)	15 – 20 psi/ 1.0 – 1.4 bar

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.

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.
When using accessory tips with this product, the instructions for use of the tips should be followed.

- **Disposal**

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

7. MARKETING AUTHORISATION HOLDER

Omrix Biopharmaceuticals NV
Leonardo Da Vinci Laan 15
B-1831 Diegem
Belgium
Tel: + 32 2 746 30 00
Fax: + 32 2 746 30 01

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/473/001
EU/1/08/473/002
EU/1/08/473/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/10/08

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Omrix Biopharmaceuticals Ltd.
MDA Blood Bank
Sheba Hospital
Ramat Gan 52621
POB 888
Kiryat Ono 55000
Israel

Name and address of the manufacturer responsible for batch release

Omrix Biopharmaceuticals NV
Leonardo Da Vinci Laan 15
B-1831 Diegem
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, Section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The Marketing Authorisation Holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted

- At the request of the European Medicines Agency

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that, at the time of the European Commission decision for this procedure (EMEA/H/C/000898/A20/0018), all users of the spray application of this product are provided with educational material. This material shall inform about the

- risk of life-threatening gas embolism if the product is sprayed incorrectly
- use of pressurized CO_2 only
- restriction to open surgery and - if the minimum spray distance of 4 cm can be accurately judged – laparoscopy
- correct pressure and distance from tissue depending on kind of surgery (open or laparoscopic)
- requirement to dry the wound using standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices) prior to using the product
- requirement to closely monitor blood pressure, pulse rate, oxygen saturation and end tidal CO_2 when spraying the product, for the occurrence of gas embolism.
- which regulator(s) should be used, in line with manufacturer recommendations and the SmPC instructions for use

The material shall include the latest Summary of Product Characteristics and the section titled “The following information is intended for medical or healthcare professionals only” of the latest package leaflet.

The MAH shall offer an educational program to all users of the spray application of this product. The program shall teach the content of the mentioned educational material.

The Marketing Authorisation Holder shall agree the exact content and format of the educational material and educational program with the national competent authority.

The MAH shall ensure that, within three months of the European Commission decision on this procedure (EMEA/H/C/000898/A20/0018), all users of the spray application of this product are provided with

- labels for the pressure regulator that inform about the correct pressures and distances in open and laparoscopic procedures
- a warning card that informs about the correct pressures and distances for the spray application for open and laparoscopic procedures
- a yellow tag, to be placed on the device air hose, which provides instructions for use. If the tag is provided as part of the medicinal product, it should be incorporated in the product information via a variation procedure

The MAH shall ensure that, within 2 years of the European Commission decision on this procedure (EMEA/H/C/000898/A20/0018), the product can only be used with a pressure regulator that caps the maximum pressure at 1.7 bars.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton box containing 2 vials

1. NAME OF THE MEDICINAL PRODUCT

EVICEL solutions for sealant

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Solutions for sealant

The active substances are as follows:
Component 1: 1 vial containing 1 ml of human clottable protein (50 – 90 mg/ml)
Component 2: 1 vial containing 1 ml of human thrombin (800 – 1200 IU/ml).

The active substances are as follows:
Component 1: 1 vial containing 2 ml of human clottable protein (50 – 90 mg/ml)
Component 2: 1 vial containing 2 ml of human thrombin (800 – 1200 IU/ml).

The active substances are as follows:
Component 1: 1 vial containing 5 ml of human clottable protein (50 – 90 mg/ml)
Component 2: 1 vial containing 5 ml of human thrombin (800 – 1200 IU/ml).

3. LIST OF EXCIPIENTS

Human Fibrinogen: arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, water for injections.

Human Thrombin: calcium chloride, human albumin, mannitol, sodium acetate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solutions for sealant

The active substances are as follows:
Component 1: 1 vial containing 1 ml of human clottable protein (50 – 90 mg/ml)
Component 2: 1 vial containing 1 ml of human thrombin (800 – 1200 IU/ml).

The active substances are as follows:
Component 1: 1 vial containing 2 ml human clottable protein (50 – 90 mg/ml)
Component 2: 1 vial containing 2 ml of human thrombin (800 – 1200 IU/ml).

The active substances are as follows:
Component 1: 1 vial containing 5 ml of human clottable protein (50 – 90 mg/ml)
Component 2: 1 vial containing 5 ml of human thrombin (800 – 1200 IU/ml).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For epilesional use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not apply intravascularly

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep upright.
Do not re-freeze once thawed.
Store in the outer carton at -18°C or colder , to protect from light. After thawing, store unopened vials in the outer carton at 2-8°C for up to 25 days starting on:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product should be discarded in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Omrix Biopharmaceuticals NV
Leonardo Da Vinci Laan 15
B-1831 Diegem

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/473/001
EU/1/08/473/002
EU/1/08/473/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Human fibrinogen:

EVICEL solutions for sealant

Component 1: Human clottable protein 50 – 90 mg/ml

2. METHOD OF ADMINISTRATION

For epilesional use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml
2 ml
5 ml

6. OTHER

To be used as two-components product with supplied device.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Human thrombin:

EVICEL solutions for sealant

Component 2: Human thrombin 800-1200 IU/ml

2. METHOD OF ADMINISTRATION

For epilesional use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml
2 ml
5 ml

6. OTHER

To be used as two-components product with supplied device.

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

EVICEL solutions for sealant
Human fibrinogen, human thrombin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell you doctor or pharmacist.

In this leaflet:

1. WHAT EVICEL IS AND WHAT IT IS USED FOR

EVICEL is a Human Fibrin Sealant which is supplied as a package containing two separate vials, each containing 1 ml, 2 ml or 5 ml of solution (Fibrinogen and Thrombin respectively) Human Fibrinogen and Human Thrombin.

An application device and appropriate accessory tips are supplied separately.

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.

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.

2. BEFORE YOU ARE TREATED WITH EVICEL

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.
- EVICEL should not be used in endoscopic surgery. For laparoscopy, see recommendations below.

Take special care with EVICEL

- To avoid the risk of potentially fatal air embolism EVICEL should be sprayed using pressurised CO_2 gas only.
- Prior to applying EVICEL, the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).

- When EVICEL is applied during surgery, the surgeon must ensure that it is only applied onto the surface of tissue. EVICEL must not be injected into tissue or blood vessels because it would cause clots which could be fatal.
- 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:
    - gluing tissues together
    - surgery to the brain or spinal cord
    - controlling bleeding in the stomach or intestines by applying the product through an endoscope (tube)
    - sealing surgical repairs to the intestines.

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

Life-threatening air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer EVICEL. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. 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 recommended by the manufacturer (see table in Section Instructions for Use). 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. Spray devices and accessory tips provide instructions for use with recommendations for pressure ranges and proximity to tissue surface, which should be carefully followed.

- Nearby areas should be protected to make sure that EVICEL is only applied onto the surface which is to be treated.

- As with any product containing proteins, allergic type hypersensitivity reactions are possible. Signs of such reactions include hives, rash, tightness of the chest, wheezing, drop in blood pressure and anaphylaxis. If these symptoms occur, the administration has to be discontinued immediately.

- When medicines are made from human blood or plasma, certain measures are put into place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of viruses/infections. Manufacturers of these products also include steps in the processing of the blood and plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses, or other types of infections.

The measures taken in the manufacture of Fibrinogen and Thrombin are considered effective for lipid coated viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus and the non-enveloped virus, hepatitis A. The measures taken may be of limited value against parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

The healthcare professionals will record the name and batch number of the medicinal product in order to trace any possible infection source.

Using other medicines
Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Pregnancy and breast-feeding
There is not enough information available to know whether any particular risks are associated with the use of EVICEL during pregnancy 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.

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

3. HOW TO USE EVICEL

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.

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 very small amounts or sprayed in short bursts (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.

4. POSSIBLE SIDE EFFECTS

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.

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

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.
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.

5. HOW TO STORE EVICEL

Keep out of the reach and sight of children.

The vials must be stored in an upright position.

Store in a freezer at -18°C or colder.

Do not use EVICEL after the expiry date which is stated on the label as well as the carton after EXP. The expiry date refers to the last day of that month.

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 25 days.

The Fibrinogen and Thrombin components are stable at room temperature for up to 24 hours but once drawn up into the application device, they must be used immediately.

6. FURTHER INFORMATION

What EVICEL contains

The active ingredients are as follows:

Component 1: Human clottable protein (50 - 90 mg/ml)
Component 2: Human thrombin (800 - 1,200 IU/ml)

Other ingredients are:

Component 1: arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride and water for injections.

Component 2: calcium chloride, human albumin, mannitol, sodium acetate and water for injections.

Pack sizes
EVICEL is available in the following sizes: 2 x 1 ml, 2 x 2 ml and 2 x 5 ml.
All packs sizes may not be marketed in all countries.

What EVICEL looks like and contents of the pack

EVICEL is a Human Fibrin Sealant which is supplied as a package containing two separate vials, 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 and Thrombin are packaged together as two vials each containing the same volume (1ml, 2ml or 5ml) of frozen, sterile solution, which is colourless or yellowish when thawed. 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.

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The following information is intended for medical or healthcare professionals only.

INSTRUCTIONS FOR USE

Read this before you open the package
EVICEL comes in sterile packages and therefore it is important to use *only* undamaged packages which have not been opened (post-sterilisation is not possible).

Preparation
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 for use in the device package. Both syringes should be filled with equal volumes, and should not contain air bubbles. Any unused product or waste material should be disposed of in accordance with local requirements. The solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

STORAGE OF EVICEL

The vials must be stored in an upright position.
Do not use after the expiry date stated on the carton and label.
Keep out of reach and sight of children.

Fibrinogen and Thrombin:

Long term storage
Store in a freezer at -18°C or colder. Do not use after the expiry date stated on the carton.

Short term storage
Store at 2°C-8°C (in a refrigerator) for no more than 25 days. The date on which refrigerator storage was started should be marked on the carton in the space provided. Do not re-freeze.

Fibrinogen and Thrombin are stable at room temperature for 24 hours but when they have been drawn up into the administration device, they must be used immediately.

Application Device:

Store separately from the Fibrinogen and Thrombin, at room temperature.

- **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 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 37ºC.

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

- **Preparation**

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

EVICEL should be applied using the CE-marked 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 are provided with the package of the application device and of the

accessory. The accessory tips should only be used by persons adequately trained in laparoscopic, laparoscopic assisted or open surgical procedures. The product should only be reconstituted and administered according to the instructions and with the devices recommended for this product.

To avoid the risk of potentially life threatening air embolism EVICEL should be sprayed using pressurised CO_2 only.

Draw the contents of the two vials into the application device, following the instructions for use in the device package. Both syringes should be filled with equal volumes, and should not contain air bubbles. No needles are involved in the preparation of EVICEL for administration.

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

- **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**

EVICEL must be sprayed using pressurised CO_2 only.

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.

When applying EVICEL using a spray device, be sure to use a pressure and a distance from tissue within the ranges recommended by the manufacturer:

Surgery	**Spray set to be used**	**Applicator tips to be used**	**Pressure regulator to be used**	**Recommended distance from target tissue**	**Recommended 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			
Laparoscopic procedures		35 cm Black Rigid Tip		4-10 cm (1.6-4 inches)	15-20 psi / 1.0-1.4 bar

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.

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.

- **Disposal**

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