

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 the 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 indicated in adults as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis (see section 5.1).

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

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 controlled 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 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 of administration

Evicel is for epileisional use.

For instructions on preparation of the medicinal product before administration, see section 6.6. The product should only be administered according to the instructions and with the devices recommended for this product (see section 6.6).

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).

To avoid the risk of potentially life-threatening air or gas embolism EVICEL should be sprayed using pressurised CO₂ gas only. For spray application see sections 4.4 and 6.6 for specific recommendations on the required pressure and distance from tissue per surgical procedure and length of applicator tip.

4.3 Contraindications

EVICEL must not be applied intravascularly.

Hypersensitivity to the active substances or to 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

EVICEL is for epileisional use only. It must not be applied 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. 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 CO₂ 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 CO₂ should be monitored because of the possibility of occurrence of a gas embolism.

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

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 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 a flexible endoscope for treatment of bleeding, or in gastrointestinal anastomoses.

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.

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.

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 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 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 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 Fertility, 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 breast-feeding women only if clearly needed.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

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.

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 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.

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Preferred Term	Frequency
<i>Adverse reactions in retroperitoneal or intra-abdominal surgery studies</i>		
Infections and infestations	Abdominal abscess Pyrexia	Common
Blood and lymphatic system disorders	Coagulopathy	Common
<i>Adverse reactions in vascular surgery study</i>		
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	Uncommon
	Wound	Uncommon
	Post procedural haematoma	Uncommon
	Post-operative wound complication	Uncommon
<i>Adverse reactions in neurosurgery study</i>		

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

Description of selected adverse reactions

Adverse reaction rates in retroperitoneal or intra-abdominal surgery studies

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.

In a study in a paediatric population involving 40 patients (20 patients treated with EVICEL and 20 controls), two adverse events (pyrexia and coagulopathy) were considered possibly related to EVICEL by the investigator.

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 non-interventional post-authorisation 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 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 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 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local haemostatics, combinations, ATC code: B02BC30

Mechanism of action

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 efficacy and safety

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.

Paediatric population

Limited paediatric data are available to support efficacy and safety of EVICEL in this population. Of 135 patients undergoing retroperitoneal and intra-abdominal surgery who were included in the controlled study of EVICEL, 4 paediatric patients were treated with EVICEL. Of these, 2 were children aged 2 and 5 years and 2 were adolescents of 16 years. In addition, a paediatric controlled clinical study evaluating the safety and effectiveness of EVICEL as an adjunct to haemostasis in soft tissue or parenchymal organ bleeding was conducted in 40 patients (20 treated with EVICEL and 20 controls). The patients age range was from 11 months to 17 years. Data from this study were consistent with results from the previous study in retroperitoneal and intra-abdominal surgery where non-inferior haemostatic efficacy of EVICEL was demonstrated.

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 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

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Within the 2 years shelf life, after thawing, unopened vials can be stored at 2°C - 8°C and protected from light, for up to 30 days. The vials can be stored at room temperature for up to 24 hours. By the end of this period the product has to be used or discarded.

6.4 Special precautions for storage

Store in a freezer at or below -18°C. Do not refreeze.

Keep the vials in the outer carton in order to protect from light.

The vials must be stored in an upright position.

For storage conditions after thawing of the medicinal product, see section 6.3. The new expiry date at 2°C-8°C should be noted on the carton but should not exceed the expiry date printed by the manufacturer on the carton and label. At the end of this period the product has to be used or discarded.

Once drawn up into the application device, the product 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 Special precautions for disposal and other handling

The instructions for use are also described in the healthcare professionals package leaflet part. The solutions are clear or slightly opalescent. Solutions that are cloudy or have deposits should not be used.

Thawing

The vials should be thawed in one of the following ways:

2°C-8°C (refrigerator): vials thaw within 1 day, or

20°C-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.

Device assembly

EVICEL should only be applied using the CE-marked EVICEL application device and optional use of accessory tips to the device. Leaflets giving detailed instructions for use of EVICEL in conjunction with the application device and optional accessory tips are provided with the package of the application device and of the accessory tips. 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 potentially life-threatening air or gas embolism EVICEL should be sprayed using pressurized CO₂ gas only (see table below).

The pressure regulator should be used in accordance with the manufacturer's instruction.

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.

When applying EVICEL using a spray device, it has to be ensured that the pressure and the distance from the tissue are within the ranges recommended by the marketing authorisation holder of this product, as given in the following table:

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 Flexible Tip	Omrix Pressure Regulator	10 – 15 cm (4 – 6 in)	20 – 25 psi (1.4 – 1.7 bar)
		35 cm Rigid Tip			
		45 cm Flexible Tip		4 – 10 cm (1.6 – 4 in)	15 – 20 psi (1.0 – 1.4 bar)
35 cm Rigid Tip					
Laparoscopic procedures		45 cm Flexible Tip		20 psi (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 CO₂ should be monitored because of the possibility of occurrence of 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 N.V.
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

Date of first authorisation: 06 October 2008
Date of latest renewal: 23 August 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR 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 SUBSTANCES AND
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Human Fibrinogen and Human Thrombin:
Omrix Biopharmaceuticals Ltd.
Plasma Fractionation Institute (Omrix-PFI)
MDA Blood Bank
Sheba Hospital
Ramat Gan 5262000
POB 888, Kiryat Ono 5510801
Israel

Human Fibrinogen:
Omrix Biopharmaceuticals Ltd.
Jerusalem Plant (Omrix-JP)
5 Kiryat Hamada St.,
Ramot Meir Building
Har-Hotzvim P.O.B. 45075
Jerusalem 9777605, Israel

Name and address of the manufacturer responsible for batch release

Omrix Biopharmaceuticals N.V.
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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

- In accordance with the European Commission decision on the procedure EMEA/H/C/000898/A20/0018 to mitigate the risk of potentially life threatening air/gas embolism when the product is sprayed at higher than recommended pressures and/or in close proximity to the tissue surface, the MAH shall ensure that:
 - When EVICEL is sprayed using pressurized gas, the gas should be carbon dioxide because the greater solubility of carbon dioxide in blood reduces the risk of embolism.
 - EVICEL is not sprayed via an endoscope when the recommended minimum safe distance from the tissue cannot be observed.
- Pressure regulators do not exceed the maximum pressure of 1.7 bars for spraying EVICEL, and contain labels stating the recommended pressure and distance.

The MAH shall ensure that 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 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 in each Member State where Evicel is marketed, all healthcare professionals who are using Evicel are provided with an educational package aiming at increasing awareness about the risk of life-threatening gas embolism if the product is sprayed incorrectly and providing guidance on how to manage that risk:

- **The educational package** should contain:
 - The Summary of Product Characteristics
 - The section titled “The following information is intended for medical or healthcare professionals only” of the latest package leaflet.
 - Healthcare professionals training material
- **The Healthcare professionals training material** shall inform about the
 - risk of life-threatening gas embolism if the product is sprayed incorrectly
 - use of pressurized CO₂ only
 - Restriction to open and laparoscopic surgeries, minimum spray distances must be observed:
 - Open surgery – minimum 10 cm
 - Laparoscopic surgery – minimum 4 cm if the spray distance can be accurately judged

- 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 CO₂ 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 exact content and format of the educational material and educational programme including communication media, distribution modalities, and any other aspects of the programme, shall be agreed with the National Competent Authority.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

EVICEL solutions for sealant
human fibrinogen, human thrombin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

1 vial containing 1 ml of human clottable protein

1 vial containing 1 ml of human thrombin

1 vial containing 2 ml human clottable protein

1 vial containing 2 ml of human thrombin

1 vial containing 5 ml of human clottable protein

1 vial containing 5 ml of human thrombin

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For epilepsional use.
Read the package leaflet before use.

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

Keep out of the sight and reach 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°C -8°C for up to 30 days starting on:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Omrix Biopharmaceuticals N.V.
Leonardo Da Vinci Laan 15
B-1831 Diegem
Belgium

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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

EVICEL solutions for sealant
human fibrinogen:
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-component 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

EVICEL solutions for sealant
human thrombin:
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-component product with supplied device.

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

EVICEL solutions for sealant

human fibrinogen
human thrombin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What EVICEL is and what it is used for
2. What you need to know before you use EVICEL
3. How to use EVICEL
4. Possible side effects
5. How to store EVICEL
6. Contents of the pack and other information

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 (Human Fibrinogen and Human Thrombin respectively).

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 in adults during surgical operations to reduce bleeding and oozing during and after the operation.

EVICEL can be used in blood vessel surgery and in surgery taking place on the posterior abdominal wall. EVICEL can also be used to support the watertight closure of the cerebral envelopes (dura mater) during neurosurgery when other surgical techniques are insufficient.

It is dripped or sprayed onto cut tissue where it forms a thin layer that seals the tissue and/or stops bleeding.

2. What you need to know before you use 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 (listed in section 6). Signs of allergic 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 must not be applied intravascularly.

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

Warnings and precautions

- To avoid the risk of potentially fatal air or gas embolism EVICEL should be sprayed using pressurised CO₂ 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 in these procedures:
 - gluing tissues together
 - surgery to the brain or spinal cord except for support of watertight closure of cerebral envelopes (dura mater)
 - controlling bleeding in the stomach or intestines by applying the product through an endoscope (tube)
 - sealing surgical repairs to the intestines
 - sealing in transphenoidal and otoneurosurgical procedures
- It is not known whether radiation therapy could affect the effectiveness of fibrin sealant when used for suture line sealing during neurosurgery.
- Use of EVICEL during neurosurgery in patients who are also being treated with implants or with dural patches has not been evaluated in clinical studies.
- The bleeding should be controlled before EVICEL is used to seal the dural suture line.
- 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 a 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 CO₂ 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.

Children and adolescents

Limited paediatric data are available to support efficacy and safety of EVICEL in this population.

Other medicines and EVICEL

Tell your doctor or pharmacist if you are taking, have recently taken, or might take 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.

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, 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, this medicine can cause side effects, although not everybody gets them. The following side effects which occurred during clinical studies were considered to be related to the use of EVICEL:

Most serious side effects

- Watery fluid coming out of your wound or nose (CSF leakage/CSF rhinorrhea)
- Headache, nausea, and vomiting (due to Subdural Hygroma, which is accumulation of CSF in the subdural space)
- Fever, or prolonged constipation, flatulence (due to abdominal abscess)

The frequency of the effects listed above was common (may affect up to 1 in 10 people).

- Numbness or pain in your extremities, change in skin colour (due to Graft Occlusion or Thrombosis)

The frequency of this effect was uncommon (may affect up to 1 in 100 people).

If you experience any of the above mentioned symptoms, or any other symptoms related to your surgery, please contact your doctor or surgeon immediately. If you feel unwell tell your doctor immediately, even if your symptoms are different from those just described.

Other side effects

Other side effects which were reported to be common during clinical trials with EVICEL (i.e., may affect up to 1 in 10 people) included meningitis, fever, difficulties with blood clotting and accumulation of CSF fluid in the brain cavities (hydrocephalus). The frequency of all of these effects was common.

Side effects which were uncommon during clinical trials with EVICEL (i.e., may affect up to 1 in 100 people) included infection, blood accumulation (haematoma), swelling, decreased haemoglobin, and post-operative wound complications (including bleeding or infection).

EVICEL is a fibrin sealant. Fibrin sealants in general may, in rare cases (up to 1 patient in 1,000 people), 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. The frequency of the type of event is not known (cannot be estimated from available data).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store EVICEL

Keep this medicine out of the sight and reach of children.

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

The vials must be stored in an upright position.

Store in a freezer at -18°C or colder. 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°C-8°C and protected from light, for up to 30 days, without being frozen again during this period. The new expiry date at 2°C-8°C should be noted on the carton but should not exceed the expiry date printed by the manufacturer on the carton and label. 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. Do not refrigerate EVICEL once it has reached room temperature.

Once drawn up into the application device, they must be used immediately. Discard unused product after 24 hours at room temperature.

6. Contents of the pack and other information

What EVICEL contains

The active ingredients are as follows:

Component 1: Human clottable protein containing mainly fibrinogen and fibronectin (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.

What EVICEL looks like and contents of the pack

Pack sizes

EVICEL is a human fibrin sealant which is supplied as a package containing two separate glass vials. Each contains 1 ml, 2 ml or 5 ml solution of human fibrinogen and human thrombin, respectively.

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

An application device and appropriate accessory tips are supplied separately.

Marketing Authorisation Holder

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for 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).

Storage

The approved shelf life of EVICEL is 2 years storage at $\leq -18^{\circ}\text{C}$. Do not use after the expiry date stated on the carton.

Within the 2 years shelf life, after thawing, unopened vials can be stored at $2^{\circ}\text{C} - 8^{\circ}\text{C}$ (in a refrigerator) and protected from light, for up to 30 days. The date on which refrigerator storage was started should be marked on the carton in the space provided. Do not re-freeze. The fibrinogen and thrombin components are stable at room temperature for up to 24 hours but when they have been drawn up into the administration device, they must be used immediately.

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 sight and reach of children.

The application device should be stored at room temperature, separately from the fibrinogen and thrombin.

Thawing

The vials should be thawed in one of the following ways:

$2^{\circ}\text{C} - 8^{\circ}\text{C}$ (refrigerator): vials thaw within 1 day,

$20^{\circ}\text{C} - 25^{\circ}\text{C}$ (room temperature): vials thaw within 1 hour,

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 $20^{\circ}\text{C} - 30^{\circ}\text{C}$.

Preparation

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 tips are provided with the package of the application device and of the accessory tips. 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 or gas embolism EVICEL should be sprayed using pressurised CO_2 only.

The solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. 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 CO₂ 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	Distance from target tissue	Spray pressure
Open surgery	EVICEL Applicator Device	6 cm flexible tip	Omrix Pressure Regulator	10 – 15 cm (4 – 6 in)	20 – 25 psi (1.4 – 1.7 bar)
		35 cm rigid tip			
		45 cm flexible tip			
Laparoscopic procedures	35 cm rigid tip	4 – 10 cm (1.6 – 4 in)		15 – 20 psi (1.0 – 1.4 bar)	
	45 cm flexible tip			20 psi (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 CO₂ should be monitored because of the possibility of occurrence of gas embolism.

Disposal

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