EVICEL®
Solutions for Fibrin Sealant

Name of the medicine

EVICEL Solutions for fibrin sealant

Description

Fibrinogen Solution. Active. 1mL contains Fibrinogen 80 to 120 mg/ml total protein (clottable protein (human) 50 – 90 mg). *Inactive.* Arginine hydrochloride, Glycine, Sodium chloride, Sodium citrate, Calcium chloride, Water for injection (WFI)

Thrombin Solution. Active. 1mL contains 800 to 1,200 IU Thrombin (human).
Inactive. Calcium chloride, Human albumin, Mannitol, Sodium acetate, Water for injection (WFI)

Note. 1 IU (international unit) Thrombin (human) is defined as the activity contained in 0.0853mg of the first international standard of human thrombin.

EVICEL® is a human plasma-derived fibrin sealant. EVICEL® is supplied as a package containing two separate vials (glass type I) with rubber stoppers (type I), each containing 2 ml or 5 ml clear or slightly opalescent solution of Fibrinogen and Thrombin (Human), respectively. The active ingredients are fractionated from pooled human plasma.

The two deep frozen solutions must be defrosted prior to use. After thawing and warming to 20-30°C, the two solutions are mixed using the application device, supplied separately (see Dosage and Administrations, below).

The Fibrinogen and Thrombin solutions appear as white to slightly yellowish opaque masses when frozen, and as clear to slightly opalescent and colourless to slightly yellowish solutions when thawed.

Chemical Structures
EVICEL Solutions for Fibrin Sealant kit is composed of 2 components, namely a preparation containing human fibrinogen (component 1), and a preparation containing human thrombin (component 2). Since these are complex compositions, chemical structure is not applicable.

Pharmacology

Pharmacodynamic properties
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 crosslinkage of fibrin.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

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.

Clinical trials

The objective of the clinical development plan was to demonstrate the haemostatic efficacy of EVICEL® in a range of surgical procedures representative of those encountered in normal clinical practice. Two Phase III prospective, randomised, controlled studies were performed in which the objective was to evaluate the haemostatic efficacy of EVICEL® by determining the proportion of patients achieving haemostasis within a pre-determined time period after application of the fibrin sealant (time to haemostasis, TTH) as compared to the control therapy.

The first study evaluated the effectiveness of EVICEL® in achieving haemostasis in soft tissue bleeding during retroperitoneal or intra-abdominal surgery as compared with a well-established haemostatic agent, oxidized, regenerated cellulose (ORC) haemostat.

The second study was conducted in patients undergoing vascular surgical procedures on an end-to-side femoral or upper extremity arterial anastomosis utilising uncoated or heparin-coated polytetrafluoroethylene (PTFE). Control patients were treated with manual compression (MC).

Table 1 Pivotal Clinical Studies Conducted with EVICEL

Study #	No. of Patients (EVICEL®/Control)	Surgical Procedure	Primary Efficacy Results (EVICEL® vs. Control)	P-Values
1	135 (66/69)	Urological Gynaecological General	95.5% vs. 81.2%	<0.05
2	147 (75/72)	Vascular	85.3% vs. 38.9%	p<0.001

EVICEL in Soft Tissue Bleeding
This was a phase III, prospective, randomised controlled clinical study to evaluate the safety and efficacy of EVICEL®. Efficacy was evaluated by the assessment of whether EVICEL® was non-inferior to ORC in achieving haemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery.

The study population comprised patients undergoing non-emergent retroperitoneal or intra-abdominal surgery procedures, wherein a soft tissue target bleeding site (TBS) was identified for which an adjunctive epilesional haemostat was indicated. Patients were stratified for age (16 years or less, and over 16 years) in order to collect data on use in paediatric patients.

The primary endpoint was haemostatic success, defined as the absence of bleeding at the TBS at 10 minutes following randomisation to treatment.

135 patients were enrolled and randomised and included in the intent to treat (ITT) analysis (66 to EVICEL, 69 to ORC). This included 11 paediatric patients aged 16 years or less.

EVICEL® (2 x 5 mL) or ORC was applied to the TBS immediately after opening the randomisation envelope. Re-application was allowed at the surgeon's discretion within the 10-minute observation period.

The results from the ITT analyses clearly showed EVICEL® to be non-inferior to the ORC, and furthermore the data indicated a significant advantage for EVICEL over ORC within 10 minutes ($p<0.05$). Kaplan Meier analysis shows that this advantage was consistent over the 10-minute period, with possibly the best advantage seen at around 2 minutes. Overall the treatment difference (log-rank test) was highly significant ($p<0.001$) in favour of EVICEL®.

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

The primary objective of the study was to evaluate whether the fibrin sealant EVICEL® reduces time to haemostasis during vascular surgical procedures on an end-to-side femoral or upper extremity arterial anastomosis utilising uncoated or heparin-coated PTFE compared to manual compression (MC).

The primary endpoint was haemostatic efficacy, defined as the absence of bleeding at the study anastomotic site (SAS) 4 minutes following randomisation to treatment. The SAS was the final anastomosis to the femoral or upper extremity artery, with the exception of the femoral-femoral procedure when the SAS was the proximal anastomosis performed as the final anastomosis in the procedure.

For each patient, one kit of EVICEL® was pre-prepared for administration prior to randomisation. A total of 147 patients were randomised. For patients randomised to EVICEL®, the required amount of product was administered by dripping onto the SAS using the application device supplied.

The primary effectiveness variable was the absence of bleeding at the SAS at 4 minutes following randomisation. The results for the full analysis set (FAS) were statistically significant in favour of EVICEL® compared to MC ($p<0.001$). This was confirmed by the per protocol (PP) set and a 'worst case' analysis. The results for upper extremity and femoral procedures were similar.

Evidence of efficacy and safety of EVICEL in vascular surgery is limited to procedures on large vessels.

Indications

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

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

Contraindications

Known hypersensitivity to the active substances or to any excipient of EVICEL®.

Injection of EVICEL® into tissues is contraindicated. Such use has been associated with inadvertent intravascular injection, with thromoembolic complications. EVICEL® should be

applied with caution to minimise any risk of intravascular application, for example in coronary bypass surgery. EVICEL® should only be applied topically.

Additionally, soft tissue injection of EVICEL® carries the risk of an anaphylactic reaction and/or local tissue damage

Precautions

Viral and Prion Risk
EVICEL® is made from human plasma. Products made from human plasma may contain infectious agents which can cause disease, such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents. 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 (HCV) and Hepatitis B Virus (HBV) and for the non-enveloped virus Hepatitis A Virus (HAV). 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.

All infections thought by a clinician possibly to have been transmitted by EVICEL® should be reported by the clinician or other healthcare provider to Johnson & Johnson Medical.

Patients should be instructed to consult their clinician if symptoms of B19 virus infection appear (fever, drowsiness, chills and runny nose, followed about two weeks later by a rash and joint pain).

General
Administration of EVICEL® may result in allergic reactions in some patients. For patients with known allergic diathesis or a history of hypersensitivity to protein products, a careful risk-benefit assessment should be carried out prior to administration.

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.

Air or gas embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening, have occurred with the use of spray devices employing a pressure regulator to administer fibrin sealants such as EVICEL®. These events appear to be related to the use of the spray device at higher than recommended pressures and in close proximity to the tissue surface.

When applying EVICEL® using a spray device, be sure to use only the pressure within the recommended pressure range by the spray device manufacturer. In the absence of a specific recommendation avoid using pressure above 20-25 psi. Do not spray closer than the distance recommended by the spray device manufacturer. In the absence of a specific recommendation avoid spraying closer than 10-15 cm from the surface of the tissue. When spraying the 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.

Adequate data are not available to support use of Evicel® in neurosurgery. In a study in rabbits, use of Evicel® to seal a lesion in the dura mater was associated with an intense inflammatory response and the development of adhesions, although it was not associated with any gross (behavioral) evidence of neurotoxicity.

Adequate data are not available to support use of EVICEL® in tissue gluing, or administration of EVICEL through a flexible endoscope for the 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.

The safety and effectiveness of EVICEL® used alone or in combination with biocompatible carriers in neurosurgical procedures or other surgeries involving confined spaces have not been established.

EVICEL® is not indicated for the treatment of massive and brisk arterial or venous bleeding. When used in these situations, EVICEL® is likely to be washed away in the flow of blood before haemostasis can be attained.

Injection into the nasal mucosa must be avoided, as severe allergic/anaphylactoid reactions have been observed and thromboembolic complications may occur in the area of the ophthalmic artery.

Effects on Fertility
The effect of EVICEL® on fertility has not been evaluated.

Use in pregnancy Category B2
The safety of fibrin sealants/haemostatics for use in humans 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 fetus, and the course of gestation. Therefore, the product should be administered to pregnant women only if clearly needed.

Use in lactation
The safety of fibrin sealants/haemostatics for use during breast-feeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to peri- and post-natal development.

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

Use in the Elderly
Clinical trials included 101 patients of 65 years of age or older (30 undergoing retroperitoneal or intra-abdominal surgery, 24 undergoing liver surgery and 47 undergoing vascular surgery). No overall differences in safety or effectiveness were observed between the elderly and younger patients. However, greater susceptibility of some older patients to adverse reactions cannot be ruled out.

Genotoxicity
Neither Fibrinogen nor Thrombin solution induces mutagenic effects in bacterial cells.

Carcinogenicity
Animal studies have not been performed to evaluate the carcinogenic potential of EVICEL.

Interactions with other medicines
No formal interaction studies have been performed. EVICEL® 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. Oxycellulose containing preparations may reduce the efficacy of EVICEL® and should not be used as carrier materials.

Adverse effects

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 events and disseminated intravascular coagulation (DIC), and there is also a risk of anaphylactic reaction.
Comparisons of adverse events for EVICEL and the comparators used in the two clinical trials are displayed in Tables 2 and 3.

TABLE 2: ADVERSE EVENTS BY MEDDRA CODED TERM WHERE AN EVENT IS EXPERIENCED BY ≥5% SUBJECTS ON ANY TREATMENT

System Organ Class	Preferred Term	Number (%)	
		Evicel (n=67)	Surgicel* (n=68)
Blood & Lymphatic System Disorders	Anaemia	3 (4.5)	4 (5.9)
Gastrointestinal Disorders	Nausea	9 (13.4)	6 (8.8)
	Vomiting	4 (5.0)	1 (1.5)
General Disorders & Administration Site Conditions	Oedema peripheral	6 (9.0)	4 (5.9)
	Pyrexia	7 (10.4)	6 (8.8)
Investigations	Haematocrit decreased	3 (4.5)	4 (5.9)
	Haemoglobin decreased	4 (6.0)	4 (5.9)
	Urine output decreased	3 (4.5)	5 (7.4)
Metabolism and Nutrition Disorders	Hyperglycaemia	2 (3.0)	5 (7.4)
	Hypokalaemia	8 (11.9)	7 (10.3)
	Hypomagnesaemia	3 (4.5)	4 (5.9)
Psychiatric Disorders	Anxiety	2 (3.0)	4 (5.9)
	Insomnia	8 (11.9)	6 (8.8)
Skin And Subcutaneous Tissue Disorders	Pruritus	5 (7.5)	5 (7.4)
Vascular Disorders	Hypertension	2 (3.0)	5 (7.4)
	Hypotension	5 (7.5)	9 (13.2)

***Surgicel = oxidised, regenerated cellulose (ORC) haemostat**

TABLE 3: ADVERSE EVENTS BY MEDDRA CODED TERM WHERE AN EVENT IS EXPERIENCED BY ≥5% SUBJECTS ON ANY TREATMENT

System Organ Class	Preferred Term	Number (%)	
		Evicel® (n=75)	MC(*) (n=72)
Blood & Lymphatic System Disorders	Anaemia	0 (0.0)	5 (6.9)
Cardiac Disorders	Cardiac Failure Congestive	0 (0.0)	5 (6.9)
Gastrointestinal Disorders	Nausea	2 (2.0)	6 (8.3)
Gastrointestinal Disorders	Constipation	2 (2.7)	5 (6.9)
General Disorders & Administration Site Conditions	Oedema Peripheral	5 (6.7)	2 (2.8)
Infections & Infestations	Urinary Tract Infection	1 (1.3)	4 (5.6)
Infections & Infestations	Graft Infection	4 (5.3)	5 (6.9)
Injury, Poisoning & Procedural Complications	Vascular Graft Occlusion	2 (2.7)	5 (6.9)
Injury, Poisoning & Procedural Complications	Graft Thrombosis	5 (6.7)	0 (0.0)
Vascular Disorders	Hypotension	1 (1.3)	5 (6.9)

(*)MC = manual compression

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

Dosage and administration

Dosage.
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 intraabdominal 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.

As an approximate guide, if a layer of 1 mm thickness is produced by applying EVICEL®, the surface areas that can be covered by each of the kit sizes are given in the following table:

Pack size	Area of Coverage via Dripping with Layer of 1 mm Thickness	Area of Coverage via Spraying with Layer of 1 mm Thickness
4 ml	8 cm2	40 cm2
10 ml	20 cm2	100 cm2

Method and route of administration

EVICEL is for epilesional use only. Before application, the surface of the wound should be as dry as possible.

Thawing:

Option 1: 37°C water bath: Transfer the frozen vials into a water bath using aseptic technique.

Approximate thawing and warming for EVICEL when using a 37°C water bath is:

Pack Size	Thawing time for 37°C water bath*
4mL	10 minutes
10 mL	10 minutes

*Vials must not be left at this temperature for longer than 10 minutes or until fully thawed. The temperature must not exceed 37ºC.

Option 2: 20-25°C (Room Temperature): Transfer vials into room temperature conditions. The approximate thawing and warming for EVICEL when placed in room temperature is:

Pack Size	20-25°C (Room Temperature)
4mL	Within 1 hour
10 mL	Within 1 hour

Option 3: 2-8°C (refrigerator): Transfer vials into a refrigerator. The approximate thawing time for EVICEL when placed in a refrigerator is:

Pack Size	2-8°C (Refrigerator)
4mL	Within 1 day
10mL	Within 1 day

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, thoracoscopic 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

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

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

Connect the female luer lock of the gas tube (with the 0.2 μm bacteriostatic filter) to a pressure regulator. The pressure regulator should be used in accordance with the manufacturer's instructions.

Information about the distance and pressure is provided in the device and tip Assembly Guides.

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 applying EVICEL® using a spray device, be sure to use only the pressure within the recommended pressure range by the spray device manufacturer. Do not spray closer than the distance recommended by the spray device manufacturer. When spraying the 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.

Overdosage

No case of overdose has been reported.

Presentation and storage conditions

Presentation
EVICEL® Solutions for Fibrin Sealant, 4mL. Composite pack containing Fibrinogen solution 2mL vial and Thrombin solution 2mL vial.

EVICEL® Solutions for Fibrin Sealant 10mL. Composite pack containing Fibrinogen solution 5mL vial and Thrombin solution 5mL vial.

An application device and appropriate accessory tips are supplied separately.

Storage
Shelf life. Deep frozen EVICEL® has a shelf life of 2 years. The vials must be stored in an upright position The expiry date is stated on the package.

Store in a freezer at or below -18^{o}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^{o}C and protected from light for up to 30 days, without being frozen again during this period. The new expiry date at 2-8^{o}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 or below 25^{o}C for up to 24 hours. Once drawn up into the application device, the solutions must be used immediately.

Name and address of the sponsor.

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EVICEL solutions for fibrin sealant
Fibrinogen, Thrombin (human) **Johnson & Johnson Medical Pty Ltd**

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

Poison schedule of the medicine

Exempt from Scheduling

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