Summary of risk management plan for EVICEL, Solutions for Sealant (human fibrinogen / human thrombin)

This is a summary of the risk management plan (RMP) for EVICEL. The RMP details important risks of EVICEL, how these risks can be minimised, and how more information will be obtained about EVICEL's risks and uncertainties (missing information).

EVICEL's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the EVICEL device should be prepared for use and the product should be applied.

This summary of the RMP for EVICEL should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of EVICEL's RMP.

I. The medicine and what it is used for

EVICEL is authorised in adults as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. EVICEL is also indicated in adults as suture support for haemostasis in vascular surgery and for suture line sealing in dura mater closure.

EVICEL contains Human Fibrinogen and Human Thrombin as the active substances and it is given by topical use only. The active substances in EVICEL are natural substances obtained from human plasma (the liquid part of the blood) and are involved in the natural blood clotting process. When the two active substances are mixed together, thrombin cuts fibrinogen up into smaller units called fibrin. The fibrin then aggregates (sticks together) and forms a fibrin clot that helps the wound to heal, preventing bleeding.

Clinical studies have shown EVICEL to be effective for treating patients/individuals undergoing surgical procedures where an haemostasis is required under abovementioned procedures. Further information about the evaluation of EVICEL benefits can be found in EVICEL's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000898/human_med_000771.jsp&mid=WC0b01ac058001d124>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of EVICEL, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status – the way a medicine is supplied to the patient (e.g. with or without a prescription) can help to minimise its risks. The instructions for use describe an outline how the device should be prepared and how the EVICEL should be applied to ensure that the medicine is used correctly;
- EVICEL can only be supplied and used by a trained physician with special training in surgical techniques to stop bleeding. EVICEL can only be used intraoperatively by the surgeon and these factors help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of EVICEL, these measures are supplemented with an additional risk minimisation measure mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities. If important information that may affect the safe use of EVICEL is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of EVICEL are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EVICEL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. use in women who are pregnant or lactating).

List of important risks and missing information	
Important identified risks	Air/gas embolism
Important potential risks	Hypersensitivity/allergic reactions, including severe anaphylaxis
	Graft occlusion complications
	Thromboembolism
	Medication error
	Tissue adhesion
Important missing information	Use in women who are pregnant or lactating

II.B Summary of important risks

Important Identified Risk: Air/Gas Embolism	
Evidence for linking the risk to the medicine	The incidence rate based on reported events and spray usage during years 2008 – 2012, was calculated to be 1/12,000 prior to implementation of risk minimization activities. Eleven (11) reports of Air/Gas Embolism have been reported with the MAHs fibrin sealant (Quixil as well as EVICEL) between 2008-2012. Three (33.3%) were fatal and six (66.6%) of the patients recovered with treatment and without sequelae.
Risk groups or risk factors	The only cases that have been reported are always associated with spray application at closer than recommended distance and/or at a higher than recommended pressure. There are no cases when EVICEL has been applied by drip.
Risk minimisation measures	The risk of air/gas embolism can be prevented by administering the spray application at the recommended distance and pressure. In addition, the risk can be further mitigated by using CO_2 gas for spray application since larger volumes of intravascular CO_2 can be tolerated as the gas dissolves much more easily than air in blood. Routine risk minimisation measures: SmPC Section 4.2 where advice is given regarding drug administration and Section 4.3 Contraindications. Section 4.4 Special Warning and Precautions. Section 6.6 Special precautions for disposal and other handling Package Leaflet Section 4.2, where information warnings and precautions is given.

Important Identified Risk: Air/Gas Embolism	
Additional pharmacovigilance activities	To mitigate cases of air/gas embolism • EVICEL should be sprayed using carbon dioxide, instead of pressurised air, because the greater solubility of carbon dioxide in blood reduces the risk of embolism; • the product information for EVICEL is updated with clear and consistent advice for healthcare professionals regarding recommended pressure and distance to use during spraying application; • EVICEL should not be sprayed via an endoscope when the recommended minimum safe distance from the tissue cannot be observed. • Pressure regulators must not exceed the maximum pressure required to deliver the EVICEL spray, and that they contain labels stating the recommended pressure and distance. Surgeons and other relevant healthcare professionals received a letter explaining these new risk-minimisation measures. In addition, they also received updated educational material from the manufacturer, reflecting the risk minimisation measures listed above.

Potential Risk: Hypersensitivity/allergic reactions, including severe anaphylaxis	
Evidence for linking the risk to the medicine	There remains a theoretical risk of hypersensitivity/allergic reactions to EVICEL due to the active substances being proteins. No cases were reported during clinical trials and only 2, highly confounded spontaneous cases have been reported to the MAH to date. Rare occurrence of Hypersensitivity/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). Isolated occurrence of severe anaphylaxis (Type I hypersensitivity), especially if the preparations is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product

Potential Risk: Hypersensitivity/allergic reactions, including severe anaphylaxis	
	Antibodies against components of fibrin sealant/haemostatic products may form rarely, due to the nature of the product. Adverse events that could be attributed to product immunogenicity may include allergic reactions, including anaphylactic reaction and/or Post-Procedural haemorrhage-lack of efficacy events
Risk groups or risk factors	Patients know to be hypersensitive to the active substances or excipients in EVICEL.
Risk minimisation measures	Do not use EVICEL in those patients known to be hypersensitive/allergic. Caution is advised when EVICEL is used for a second or subsequent surgery.
Additional pharmacovigilance activities	None

Potential Risk: Graft occlusion complications	
Evidence for linking the risk to the medicine	There is no evidence from clinical trials or post-marketing experience that EVICEL results in an increased incidence of graft occlusion compared to other methods used to reduce bleeding from graft anastomoses or the background occurrence of occlusion following grafting. It is theoretically possible that use of EVICEL around the site of a graft anastomosis may cause introduction of Human Thrombin and Human Fibrinogen or clot itself to enter the graft and either cause occlusion directly or via activation of clotting pathways. Acute graft occlusion may produce clear cut ischaemic symptoms, though these normally subside rapidly allowing for an elective approach to treatment, which may involve hospitalisation, thrombolytic therapy, and anticoagulation. Rarely, ischaemia fails to respond and urgent revascularisation with re-grafting is necessary.
Risk groups or risk factors	No data available
Risk minimisation measures	None
Additional pharmacovigilance activities	None

Potential Risk: Thromboembolism	
Evidence for linking the risk to the medicine	There have been rare case reports of thromboembolism, including pulmonary embolism, associated with the use of fibrin sealants. Product embolism was not suspected in these cases. The background incidence of thromboembolism following a range of surgery types is approximately 0.8%, of which approximately a third were pulmonary embolism.
Risk groups or risk factors	If product embolism occurred then it could theoretically lead to a fatal pulmonary embolism.
Risk minimisation measures	Avoid inadvertent intravascular injection
Additional pharmacovigilance activities	None

Potential Risk: Medication error	
Evidence for linking the risk to the medicine	Two types of medication error can be envisaged. Firstly, inadvertent intravascular injection, which could lead to product embolism (discussed separately), or incorrect mixing of the thrombin and fibrinogen components leading to lack of or poor clot formation at the desired site with resultant lack of efficacy.
Risk groups or risk factors	There are no known risk factors.
Risk minimisation measures	Clear instructions are given already in the SmPC.
Additional pharmacovigilance activities	None
Potential Risk: Tissue Adhesion	
Evidence for linking the risk to the medicine	Theoretically, application of EVICEL away from the intended area, particularly in larger quantities, could lead to unwanted tissue adhesion. The surgeon should be aware this has occurred and can take remedial action at the time and no consequences are likely. However, even if used at the intended site, it is theoretically possible that unwanted adhesion to surrounding tissue may occur. Again, given the rapidity of achieving sufficient adhesion strength with fibrin sealants (30 seconds or less), it is likely that adherence of the treated tissue to another will be noticed by the surgeon and remedial action taken. No data available
Risk groups or risk factors	No data available

Risk minimisation measures	Routine risk minimisation measures: Section 4.4 of the SmPC warns the surgeon to protect (by covering) areas outside the intended treatment area to avoid unwanted tissue adhesion.
Additional pharmacovigilance activities	None

Missing information Use in pregnancy and lactation	
Evidence for linking the risk to the medicine	EVICEL was not studied in women who are pregnant or lactating. There is no reason to believe that results in women who are pregnant or lactating would be any different than in any other adult.
Risk factors and risk groups	A risk associated with use cannot be defined based on available evidence.
Risk minimisation measures	Routine risk minimisation methods: Routine pharmacovigilance via spontaneous ADR reporting Additional risk minimisation methods: No risk minimisation methods
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of EVICEL Solutions for Sealant.

II.C.2 Other studies in post-authorisation development plan

A non-interventional post-authorisation safety surveillance 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.