



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Fibrin haemostatic agent/sealant

Proprietary Product Name: Evicel

Sponsor: Johnson & Johnson Medical Pty Ltd

**December 2012**

**TGA** Health Safety  
Regulation

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- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <[www.tga.gov.au](http://www.tga.gov.au)>.

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# I. Introduction to product submission

## Submission details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	10 October 2012
<i>Active ingredient(s):</i>	Fibrin haemostatic agent/sealant
<i>Product Name(s):</i>	Evicel
<i>Sponsor's Name and Address:</i>	Johnson & Johnson Medical Pty Ltd 1-5 Khartoum Road North Ryde NSW 2113
<i>Dose form(s):</i>	Two deep frozen solutions
<i>Strength(s):</i>	2 mL and 5mL of each solution
<i>Container(s):</i>	Both Fibrinogen Solution and Thrombin Solution are contained in two separate glass vials and delivered via separate chambers of a single use double chamber syringe made of polypropylene.
<i>Pack size(s):</i>	4 mL and 10 mL
<i>Approved Therapeutic use:</i>	As supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.  As suture support for haemostasis in large vessel vascular surgery.
<i>Route(s) of administration:</i>	Topical
<i>Dosage:</i>	Evicel Fibrin Sealant (Human) should be sprayed or dripped onto the tissue in short bursts (0.1-0.2 mL) to produce a thin, even layer. If the hemostatic effect is not complete, a second layer should be applied. The amount of Evicel required depends upon the area of tissue to be treated and the method of application.
<i>ARTG Number (s)</i>	4 mL : 181318 (4 mL) and 181319 (10 mL)

## Product background

Evicel comprises a vial containing fibrinogen (clottable protein) and a separate vial containing thrombin, both as frozen solutions and both derived from human plasma (US donors). When the contents of the two vials are thawed and mixed (1:1 ratio, *via* a device to be assessed separately within the TGA) thrombin activates fibrinogen to form a fibrin clot that adheres to wound surfaces, providing a matrix for cell migration until connective tissue is regenerated. The sealant (along with its associated ingredients and excipients) is degraded in the natural course of wound healing by cells with fibrinolytic and phagocytotic activity that migrate into the sealant.

Ingredients in the two solutions include the following:

1. "Fibrinogen solution"

- Fibrinogen (Clottable Protein) (human) 50 - 90 mg per mL Coagulation factor
- Factor XIII (human) 2 - 15 IU per mL Coagulation factor

2. "Thrombin solution"

- Thrombin (human) 800 – 1,200 IU per mL Coagulation factor
- Calcium chloride 5.6 – 6.2 mg per mL Clotting activator

This AusPAR describes the evaluation of an application by Johnson & Johnson Medical Pty Ltd (the sponsor) to market two presentations of the product containing 2.0 or 5.0 mL of each solution.

There are two other fibrin sealant/adhesive/haemostatic agent products registered in Australia: Tisseel and Artiss.<sup>1,2</sup>

The sponsor sought approval for two indications:

- *A general surgical haemostasis indication for situations in which standard surgical techniques are insufficient.*
- *As suture support for haemostasis in large vessel vascular surgery.*

The latter indication is similar to that currently approved for Tisseel:

- *A specific indication for use as suture support in vascular surgery.*

## Regulatory status

A similar application has been approved in the USA in June 2006, the European Union (EU)<sup>3</sup> in October 2008 and Switzerland in November 2010. An application in New Zealand was pending at the time of this AusPAR. The indication worldwide is:

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

<sup>1</sup> TGA, AusPAR for Fibrin sealant (Tisseel), April 2010. Available from <http://www.tga.gov.au/pdf/auspar/auspar-tisseel-vhsd.pdf>

<sup>2</sup> TGA, AusPAR for Fibrin sealant (Artiss), October 2010. Available from <http://www.tga.gov.au/pdf/auspar/auspar-tisseel-vhsd.pdf>

<sup>3</sup> Centralised procedure: 27 Countries of the European Medicines Agency (EMA) and+ 3 countries of the European Free Trade Association (EFTA).

**Product Information**

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

**II. Quality findings****Drug substance (active ingredient)**

Evicel is a Fibrin Sealant Kit according to the relevant European Pharmacopoeia monograph. It consists of two human plasma derived components, Component 1 (fibrinogen concentrate) and Component 2 (thrombin preparation), each presented in a separate vial. The components are supplied together as a composite pack (see *Presentation and composition* below for further details). When the two components are combined, the thrombin cleaves the fibrinogen resulting in the formation of a fibrin clot. The product is manufactured by OMRIX Biopharmaceuticals.

The plasma source for the product is described in the OMRIX Biopharmaceuticals Plasma Master File. Plasma is collected at commercial collection facilities in the USA from remunerated plasmapheresis donors. The OMRIX PMF has not been previously evaluated by the TGA and is also evaluated as a part of this submission. The human albumin used in the formulation of Component 2 (thrombin preparation) is purchased from Talecris Biotherapeutics Inc.. The plasma used for the manufacture of the albumin is described in the Talecris Plasma Master File, which has been previously reviewed by the TGA and accepted.

Viral inactivation steps used in the manufacture of the components are:

- Component 1 (fibrinogen concentrate) - solvent detergent treatment and Pasteurisation
- Component 2 (thrombin preparation) – solvent detergent treatment and nanofiltration.

The viral safety aspects of the albumin used was reviewed as a part of this application and found acceptable.

**Drug product**

As previously noted in this AusPAR, there are currently two other Fibrin Sealant kits in the Australian Register of Therapeutic Goods (ARTG) and details of these and Evicel are shown in Table 1.

**Table 1: Comparison of fibrin sealant products**

Product	Component 1 (fibrinogen concentrate)	Component 2 (thrombin preparation)	Other
<b>Evicel</b>	Total Protein 80-120 mg/mL Clottable Protein 50-90 mg/mL Factor XIII 2-15 IU/mL	Thrombin 800-1,200 IU/mL CaCl <sub>2</sub> 5.6-6.2 mg/mL Albumin 5.0-6.5 mg/mL	Plasminogen is removed from the Component 1 rather than addition of the fibrinolysis inhibitor aprotinin. Storage -18°C 2 years
<b>Tisseel VH SD</b>	Fibrinogen 72 mg/mL Aprotinin 3000 KIU/mL Factor XIII 1.2 IU/mL Albumin 10 mg/mL	Thrombin 500 U/mL CaCl <sub>2</sub> 40 micromole/mL Albumin 45 mg/mL	Storage -18°C 2 years
<b>Artiss</b>	Fibrinogen 72mg/mL Aprotinin 2250 KIU/mL Factor XIII 1.2IU Albumin 10mg/mL	Thrombin 3.2 IU/mL CaCl <sub>2</sub> 36 micromole/mL Albumin 45mg/mL	Storage -18°C 2 years Aprotinin component is synthetic

### Predecessor product

Evicel is the second generation of the fibrin sealant kit Quixil (Crosseal in the USA) manufactured by OMRIX. The first generation product Quixil has not been registered in Australia. The major differences between Quixil and Evicel are in Component 1 (fibrinogen concentrate), where in the final step of manufacture of this component for Evicel, plasminogen is removed by chromatography on a column of immobilised tranexamic acid. In Quixil the fibrinogen component is stabilised by tranexamic acid (10% weight/volume (w/v)) (a synthetic fibrinolysis inhibitor that inhibits plasminogen).

Tranexamic acid is potentially neurotoxic, which contraindicates the use of Quixil for use in neurosurgery. By specific removal of plasminogen during the manufacture of Evicel Component 1 (fibrinogen concentrate) the need to use tranexamic acid for stabilisation of Component 1 is avoided.

### Presentation and composition

Evicel fibrin sealant is supplied as a composite pack frozen (-18°C) containing the two separate components, each presented in a separate vial closed with a rubber stopper and an aluminium crimp seal. The components are ready to use upon thawing. The components are combined upon application to the surface of a surgical wound using an application device that will be supplied separately. There are two modes of application for Evicel described in the proposed PI, application by dripping and spray application, each using the same application device, the second using pressurised carbon dioxide (CO<sub>2</sub>) or pressurised air delivered through an auxiliary tube to form a spray of the product.

There are two presentations of this product; 2 mL and 5 mL (Table 2).



**Table 2A: Composition of Component 1**

Presentation size/ingredient	1 mL	2 mL	5 mL
<b>Component 1 (fibrinogen concentrate)</b>			
Fibrinogen (Clottable Protein)	50-90 mg	100-180 mg	250-450 mg
Factor XIII*	2-15 IU	4-30 IU	10-75 IU

**Table 2B: Composition of Component 2**

<b>Component 2 (thrombin preparation)</b>			
Thrombin – human	800-1,200 IU	1,600-2,400 IU	4,000-6,000 IU
Calcium chloride	5.6-6.2 mg	11.2-12.4 mg	28-31 mg
Albumin-human	5.0-6.5 mg	10-13 mg	25-32.5 mg

The sponsor withdrew their application for a 1 mL presentation of the product.

### Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is not photostable.

### Shelf-life conditions

It was recommended that the approved shelf-life for Evicel fibrin sealant for 2 mL and 5 mL sizes is:

- 2 years, store at or below -18°C (Deep Freeze)

Additional storage information includes:

- After thawing, unopened vials can be stored at 2-8°C, protected from light for up to 30 days without being frozen again during this period. 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°C for up to 24 hours. Once drawn up into the application device, the solutions must be used immediately.

### Bioavailability

This application was reviewed at the 136th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The committee had no objection on quality and pharmaceutical grounds to approving the application to register Evicel provided all the outstanding issues were addressed to the satisfaction of the TGA.

**Advisory committee considerations**

The following additional issues were raised by the PSC and were required to be addressed by the sponsor<sup>4</sup>:

- a. The consequences (if any) of using the product without complete thawing or at temperatures lower than described.
- b. How the date and time of thawing should be recorded
- c. Where the product should be stored (for example, in a monitored refrigerator suitable for blood components) after thawing and the necessity of storing thawed product.

It was noted that the related products Tisseel VH S/D and Artiss have much more detail included in the Product Information (PI) with regards to this and the sponsor was recommended to amend the information to more clearly indicate storage after thawing.

The committee also noted the following statement in the PI:

“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.”

Although the PSC considered this statement appropriate, the committee was however of a consensus that this information would not be easily retrieved in the event of a “look back” for infectious or any other reasons. The PSC therefore recommended that appropriate traceability procedures be implemented.

The evaluator noted that there should be consistency between what is requested with regard to this product and similar products in the ARTG. The committee made no such recommendation with regard to Tisseel VH S/D or Artiss and the PI’s for these products do not contain a similar warning. All these products have the same issues as they are derived from human plasma. It is accepted practice that batch numbers of product are recorded when human derived plasma products are administered to facilitate look back should it be required.

Various mechanisms exist to facilitate this, a common one is that a removable sections is included on the container labels which includes the batch number and product name which may removed and stuck to the patients records. The clinical evaluator should note that there needs to be consistency across the product range.

All other issues outstanding at the time of the PSC consideration were satisfactorily resolved.

**Quality summary and conclusions**

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application were evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The following issues of concern were noted:

- The clinical evaluator’s attention was requested to the comments at the beginning of this evaluation with regard to consistency with regard to the PI for this class of products.

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<sup>4</sup> Sponsor comment: “These issues were addressed by the sponsor.”

- Clarification of the wording in the PI with regard to the storage of the product after thawing but prior to use
- Good Manufacturing Practice (GMP) clearances were at the time of this quality report outstanding for a number of facilities.<sup>5</sup>
- The sponsor was requested to submit an application for the inclusion of the delivery device in the ARTG. This should be approved prior to the registration of this product.

It was recommended that it be a condition of registration that the first five independent batches of Evicel fibrinogen and thrombin 2 mL and 5 mL solution for sealant vials imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

### III. Nonclinical findings

#### Introduction

Evicel is based on a formulation that has been registered in overseas countries (but never in Australia) since the late 1990s under the trade names Quixil and Crosseal (the name Quixil is used consistently in this report). The fibrinogen component of Quixil includes the antifibrinolytic agent tranexamic acid, which is included to inhibit plasminogen (precursor for the fibrinolytic enzyme, plasmin) also present in the formulation. However, tranexamic acid is a known neurotoxin and therefore the sponsor has reformulated the fibrinogen component of Quixil to remove both plasminogen and tranexamic acid, and, by necessity, to increase the content of clottable protein. The same thrombin component of Quixil is used for Evicel.

Because of the similarities between Evicel and its predecessor Quixil, only a bridging program was undertaken with Evicel, mainly to establish whether there are safety and efficacy differences between the two formulations. However, for this application, the sponsor has also submitted the earlier nonclinical studies conducted to support the (overseas) registration of Quixil. These are relevant to the current application because the differences in the fibrinogen component between Evicel and Quixil are not substantial from a toxicological viewpoint<sup>6</sup>.

Nonclinical studies focussed on local tissue responses after a single epilesional application of Evicel or Quixil to surgically dissected tissues in rats, rabbits and domestic pigs. Conventional nonclinical studies with products such as Evicel are not possible because species-specific immune responses to human proteins would confound repeat dose findings. However, the nonclinical data package for this application adequately addressed product efficacy, comparative efficacy and local tolerance at a variety of tissue sites after a single application. The quality of some of the nonclinical studies and/or reports was less than adequate according to current regulatory standards, however, the overall package was sufficient given the nature of the product and its intended clinical use. It was also acknowledged that there is substantial post marketing experience with the predecessor product Quixil, which diminishes the need for extensive nonclinical investigations with Evicel.

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<sup>5</sup> Sponsor comment: "This issue has been addressed."

<sup>6</sup> Sponsor comment: "Other than the removal of the potentially neurotoxic chemical tranexamic acid from Evicel."

The nonclinical data included several studies investigating the toxicity of tri-n-butyl-phosphate (TNBP) and Triton X-100, which are residual solvent impurities arising from viral inactivation processes for the (human plasma sourced) fibrinogen and thrombin components. All of these studies have previously been submitted and evaluated on several occasions by the TGA and have not been re-evaluated for this application. These studies, as well as additional safety information on TNBP and Triton X-100 evaluated previously by the TGA, were sufficient to allow assessment of whether these impurities posed any safety issues at the proposed limits of 5 µg/mL for each substance in both the fibrinogen and thrombin components of Evicel (see below).

## **Pharmacology**

### **Primary pharmacodynamics**

Studies confirming that the thrombin and fibrinogen concentrations in Evicel are optimal were done in rats with bisected kidney and in rabbits with dissected liver, respectively. When compared with concentrations in the proposed Evicel formulation, a decrease in thrombin concentration resulted in increased bleeding time, while a decrease in clottable protein content resulted in decreased clot strength/cohesion properties.

The efficacy of the Evicel predecessor formulation Quixil as a tissue haemostat was assessed in three rabbit liver dissection studies and in a rat pancreatic dissection study. Wound haemostasis (assessed by bleeding time) was 6-11 times more rapid and blood loss was negligible if Quixil was applied than if the wound was left untreated, which supports the rationale behind the use of fibrinogen/thrombin products to facilitate haemostasis.

Several comparator studies showed that the tissue haemostasis effect of Evicel does not substantially differ from that of Quixil. These involved a range of dissected tissues (rat kidney, rabbit liver, rat abdominal wall) and there was no evidence for substantial differences in haemostasis properties between the products. In the rat abdominal wall defect model, Evicel was also comparable to two other commercially available fibrin sealants - Tissucol and Tisseel - in terms of 'clot half-life' based on residual clot weight or residual clottable protein content; a clot half-life of 2.6-4.8 days was estimated for these products with no significant differences between products.

A primary pharmacology study of Evicel in pigs was of particular interest and relevance because the pigs were of similar size to an average human (around 70 kg) and the full 10 mL volume of sealant could be applied by dripping or spraying onto liver biopsy sites (x 4), using laparoscopic techniques. The outcomes, ease of Evicel use and accuracy of application during laparoscopic application were compared with those from an identical study using open surgery techniques and a standard catheter tip to deliver Evicel (by spraying or dripping).

The operators reported no difficulties or control problems when dripping or spraying Evicel laparoscopically onto liver biopsy sites. The solution was able to be restricted to the intended site in almost all cases; the spray extended beyond the intended site in a few cases during laparoscopic surgery but this was attributed to errors in the positioning guides rather than to an inherent fault of the Evicel device. Complete haemostasis occurred within 3 minutes (min) under almost all conditions in both the open and laparoscopic studies and no untoward effects were reported.

Overall, the primary pharmacology studies adequately demonstrated that Evicel provides effective tissue haemostasis in situations that mimic its intended clinical use. No animal treated with Evicel died due to haemorrhage in the nonclinical development program, compared with 1 or 2 untreated controls or Quixil treated animals. There was adequate

evidence for pharmacological equivalence between Evicel and Quixil, which contributes to the validity of using toxicity studies with Quixil to support the safety of Evicel.

## **Toxicology**

### **Local tolerance – peripheral tissues**

A variety of dissected tissues treated with Quixil and tissues in the immediate vicinity of the dissected sites were examined macro and/or microscopically in several studies, many of which included a comparison of dissected tissue sites that were left untreated.

Dissected tissues included: liver in rabbits; and pancreas, kidney, lung, aorta, bone (femoral epiphysis), and stomach mucosa in rats. Animals were observed for periods ranging from 1 to 4 weeks following the surgical procedure; no in-life adverse effects were reported in any study, which provides reassurance for the absence of systemic effects.

In all studies, local tissue responses were consistent with tissue healing and degradation of clot/sealant material. There was no evidence for re-bleeding or for local and adjacent tissue intolerance. Adhesions between the operated site and adjacent tissues were observed in some cases and these sometimes differed in location from those in controls; however, adhesions are an anticipated outcome of surgery and the use of tissue sealant did not appear to substantially increase the risks in animals.

Although these studies used Quixil, the findings remain valid for Evicel because the differences between the fibrinogen components of the two formulations are not expected to result in differences in toxicity profile between the two products. Further, tissue responses after liver surgery in rabbits were qualitatively similar in a local tolerance study comparing Evicel and Quixil: no evidence for adverse effects with either substance was found in this study.

### **Local tolerance – central and peripheral nervous tissues**

The Evicel predecessor formulation Quixil was precluded in neurosurgery and in procedures where contact with the cerebral spinal fluid (CSF) or dura mater might occur because of potential neurotoxicity (sometimes fatal) due to tranexamic acid. Evicel does not contain tranexamic acid and there was no obvious evidence for gross neurological (behavioural) impairment over a 14 day recovery period after Evicel was used to seal a lesion in the dura mater in rabbits. However, changes in the rabbit dura mater (extending to the dura pia) after Evicel treatment substantially differed from those occurring (in the dura mater only) during normal healing processes in untreated rabbits.

At 14 days after a bilateral defect was made in the dura mater, 7 of 17 (41%) CSF samples from Evicel treated rabbits were described as having 'discrete inflammation' characteristics or 'subnormal' characteristics, compared with none of 8 samples from untreated rabbits, which were all described as having 'absence of inflammation and [not] subnormal' characteristics.

Lesioned areas in controls were unremarkable and "filled with tissue", whereas those in Evicel treated rabbits included areas of liquid accumulation/seroma formation and showed an acute, intense inflammatory response at the application tissue interface, with numerous polymorphonuclear neutrophils, lymphocytes and macrophages infiltrating bands of fibrous tissue. The inflammatory response was reported to extend outside the dissected area, along all of the soft tissue covering the cranium. The fibrous tissue merged with the dura mater so that the latter was no longer distinguishable. Severe and extensive adhesions were present at the site of the dissection and these spanned the entire craniotomy site and involved the dura mater, pia mater and other soft tissues. The sealant

product was suspected to have 'moved' in one rabbit; and it was reported to have degraded little over the 14 day period after surgery.

The tissue changes 14 day post surgery in controls appeared very different: there was little or no inflammatory response, only mild tissue changes at the defect site and a more localised healing process.

Changes in the cerebral cortex were similar in controls and Evicel treated rats and any that were present appeared to be associated with the surgical procedure. As mentioned above, there was no gross evidence for adverse central nervous system (CNS) effects during the life in this study. However, the significance and any long term consequences of the tissue changes in the CNS after Evicel treatment in the rabbit study are not clear and would need to be further investigated if Evicel was to be used for procedures involving exposure to CNS tissues.

A study in rats investigated the effects of Quixil on peripheral nervous tissue (sciatic nerve) 4 weeks after surgery. No notable findings were reported at operated sites in untreated rats. In Quixil treated rats, the lesioned sites showed slight neovascularisation, peri-nervous granuloma (2 mm; at 1 site only) and presence of blood vessels, macrophages, fibrocytes and lymphocytes but no residual sealant material. The response is consistent with tissue healing; the fact that it was considerably more prolonged than in controls raises some concern and reinforces the need to conduct further investigations if Evicel was to be used in neurosurgery.

### **Systemic toxicity and other toxicity studies with Quixil or Evicel**

As mentioned above, a full nonclinical development program with Evicel and similar products was not possible. However, some studies in addition to the efficacy and local tolerance studies described above have been conducted with Evicel and/or Quixil.

To assess the potential for systemic toxicity and for toxicity at tissues and organs distant from the site of application, gross and microscopic assessment of all tissues was done in two rabbit liver dissection studies – one where the liver lesions were treated with Quixil or Evicel, and the other where they were treated with Quixil or no treatment, respectively. There were no notable findings except at tissues involved in the operation. Further reassurance about the lack of potential for systemic toxicity is derived from the lack of in-life findings during the 1-4 weeks observation periods in the local tolerance studies. Lack of evidence for systemic toxicity is not unexpected following local administration of Evicel.

Other studies conducted with Quixil (that remain relevant to Evicel) comprised bacterial gene mutation studies with the fibrinogen and thrombin components (both negative, as expected), pharmacokinetic studies assessing the elimination kinetics of thrombin related radioactivity and ocular and skin irritation assessments in rabbits.

The thrombin pharmacokinetic studies impact on potential toxicity indirectly because of the potential for thrombosis if sufficient concentrations of thrombin enter the circulation after application of Evicel (which has the same thrombin formulation as Quixil). Based on the findings in the rabbit study, systemic concentrations of thrombin after episomal application of Evicel would be about 2% of the applied thrombin dose applied, which is reported to be similar to that generated endogenously by a minor bleeding episode and which is unlikely to increase the risk of thrombogenesis.

Quixil was found to have no or slight potential for causing skin and eye irritation, which is important information in case of accidental exposure of these sites by either the patient or operators. It was noted that the draft PI includes recommended steps to avoid unnecessary exposure.

### **Toxicity studies with solvent residues**

Both the fibrinogen and thrombin component of Evicel are derived from human donor plasma and are required to undergo viral inactivation during the manufacturing process. Solvent/detergent treatment with TNBP and Tritox X-100 was used for this purpose during the manufacture of Evicel. This is a common practice for inactivating enveloped viruses in plasma derived products and is recognised by regulatory agencies including the TGA.<sup>7</sup>

Proposed limits are not more than (NMT) 5 µg/mL for TNBP and NMT 5 µg for Triton X-100 in each of the Evicel vials. If both vials of the highest proposed pack size are used (10 mL total volume), the human 'dose' of TNBP and Triton X-100 solvent would be about 0.5 µg/kg, or 16.5 µg/m<sup>2</sup> for a 50 kg human and only a small portion of this would be expected to enter the systemic circulation after epilesional administration at any one time.

Elimination of solvents residing in the fibrin clot would be expected to be similar to the processes involved in degrading the other components of the clot matrix.

The sponsor submitted several studies to justify the safety of TNBP and Triton X-100 at the proposed limits. These have not been re-evaluated because they, along with other information on these agents, have been considered by the TGA on several occasions in the course of assessing the safety of residual solvent limits for a number of registered plasma derived products.

On the basis of previous safety assessments, there are no concerns on nonclinical grounds over the proposed limits of 5 µg/mL for TNBP and 5 µg/mL for Triton X in each Evicel vial. At these concentrations, the doses expected to be delivered to humans are substantially lower than the doses delivered *via* a number of systemically administered plasma derived products that contain these residual solvents. Local tolerance issues with these solvents is not anticipated to be a concern over and above those with Evicel (or Quixil) itself, because the finished product containing these solvents was used in the preclinical program and/or has been on the market overseas for some time.

### **Nonclinical summary and conclusions**

Conventional nonclinical studies with products such as Evicel are not possible because species-specific immune responses to human proteins would confound repeat dose findings. However, the nonclinical data package adequately addressed product efficacy, comparative efficacy and local tolerance at a variety of tissue sites. There was also adequate investigation of potential systemic toxicity, including thrombogenesis: no evidence for systemic toxicity was found in animal studies after epilesional application of the proposed product or a related product.

Nonclinical studies provided adequate evidence to support the use of Evicel for reducing bleeding time and blood loss when applied epilesionally to a variety of dissected peripheral tissues in animals. There was no evidence for local adverse effects or systemic toxicity when Evicel (or a comparable formulation) was applied to peripheral tissues. However, a more intense and prolonged inflammatory response was found in the CNS and in peripheral nervous tissue after Evicel was applied than if the lesions were left to heal spontaneously. The significance of the changes in rabbit dura after application of Evicel were not fully explored; however, they are very different from the control (untreated) healing process and warrant further investigation if Evicel is ever to be used for neurosurgery.

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<sup>7</sup> European Medicines Agency. Committee for Medicinal Products for Human Use. 25 January 2001. Note for Guidance on Plasma Derived Medicinal Products, CPMP/BWP/269/95 Rev 3.

Although Evicel is not proposed for use in neurosurgery, it was recommended that there are strong precautions against its use in this type of surgery until extensive investigations are done to establish the safe use of the product in this setting.

Proposed limits for residual solvents used for viral inactivation of plasma-derived substances are 5 µg/mL for tri-n-butyl-phosphate and 5 µg/mL for Triton X-100, in each Evicel vial. There are no safety concerns arising from these substances at the limits proposed.

Based on findings in the rabbit CNS local tolerance study where the tissue response after Evicel application included a prolonged inflammatory component and differed markedly from spontaneous healing, it was recommended that consideration be given to contraindicating the use of Evicel in neurosurgery until there is further investigation and reassurance of its safe use in this setting.

Findings in animal studies do not indicate cause for concern over the registration of Evicel for the indications proposed.

### **Evaluator's summary of the sponsor response to the nonclinical evaluation report**

In response to the above recommendation, the sponsor suggested there is no reason to contraindicate the use of Evicel in neurosurgery, based on: the lack of treatment related signs of neurotoxicity in the rabbit study; findings of comparable effects between Evicel, Duraseal and Tisseel in a (previously unsubmitted) dog dural defect study (see below); and recent approval to commence clinical trials of Evicel in neurosurgery in the UK, Germany, Finland and Netherlands.

In relation to findings of a more severe and prolonged local inflammatory reaction in Evicel-treated rabbits than in sham controls (from a previously submitted study), the sponsor suggested this was due to *"the xenogenic proteins, which were not present in the sham group."* Evicel is derived from human plasma proteins and therefore this is a reasonable explanation for the response in treated rabbits. However, it also highlights the limitations of the rabbit study and emphasises the need to conduct further, appropriate studies before Evicel is considered for neurosurgery in humans.

The newly submitted study in dogs showed substantially comparable effects between Evicel, Duraseal (not on the ARTG) and Tisseel (registered in Australia, but according to its PI, *'should not be used for the sealing of neuroanastomoses'*) when used to prevent CSF leakage from a 2 cm dural defect in mongrel dogs (9/group). This study (finalised in 2008) was not included in the original application but the sponsor was not seeking to register Evicel for use in neurosurgery and therefore it is not pivotal to this application.

### **Evaluator comment**

The dog study has not been formally submitted as supplementary data and therefore it was considered only in the context of whether or not it supports the recommendation in the nonclinical evaluation report that *'consideration be given to contraindicating the use of Evicel in neurosurgery until there is further investigation and reassurance of its safe use in this setting.'* On this basis, there were no findings that justify a stronger recommendation that consideration be given to contraindicating Evicel in neurosurgery, from a nonclinical viewpoint. The study has not been evaluated in the context of a proposal for use in neurosurgery.

The new dog study should be submitted for formal evaluation by the TGA as part of any future application to register Evicel for use in neurosurgery.



## IV. Clinical findings

### Introduction

The sponsor has conducted and provided data for two randomised controlled trials (RCTs) in order to explore the proposed indications (400-05-06 and 400-05-01). Study 400-05-06 used broad inclusion criteria and studied a variety of surgical specialties (urology, gynaecology and general surgery), so the outcomes may be broadly generalised to surgical patients. Study 400-05-01 enrolled and studied only vascular patients to inform upon this aspect of the proposed indication.

Evicel is promoted as a supportive, rather than front line treatment to obtain haemostasis. The sponsor did not define the length of time that Evicel is expected to provide haemostasis for but noted that after application, absorption of thrombin into the plasma is slow. In the pivotal clinical studies clinicians used techniques such as sutures, ligation or cautery to attempt haemostasis prior to applying Evicel. Both studies used haemostasis as their primary outcome measure and further explored time to haemostasis as subgroup analyses.

The required volume and frequency of Evicel application will depend upon the patient's clinical needs. In the pivotal trial in vascular surgery the individual dose administered was up to 4 mL, whereas in the pivotal trial in retroperitoneal or intra-abdominal surgery trial the individual dosage ranged from 0.5 to 10 mL. In some surgical situations larger volumes of Evicel may be required to achieve haemostasis; however, the safety and efficacy of doses larger than 10 mL have not been assessed in clinical studies.

Evicel can be applied by dripping or spraying onto tissue. Neither pivotal study performed subgroup analysis according to application method.<sup>8</sup>When spraying Evicel an additional spray applicator is required and the proposed Australian PI suggests that a variety of spray applicators are available, which may have introduced further variability into the observed safety and efficacy outcomes.

The sponsor states that no development program was in place for the use of Evicel in paediatric patients at the time of submission. The sponsor advised that the clotting mechanism of Evicel is identical for both adults and children, which was confirmed by the clinical evaluator. One pivotal study (400-05-06) performed a subgroup analysis in paediatrics patients ( $\leq 16$  years). This study also performed subgroup analyses for adults aged over 65 years. A summary of the ages of patients studied in the pivotal studies is shown in Table 3. Although Study 400-05-01 included 89 patients aged 65 or over, no subgroup analysis was conducted.

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<sup>8</sup> Sponsor comment: "Evicel was dripped in the PV study, sprayed in all but one patient in the Neuro study whereas the RP study allowed both drip and spray."

**Table 3: Ages of patients enrolled in pivotal studies**

Category		Study 400-05-006 (n=135)	Study 400-05-001 (n=147)
<b>Age (years)</b>	Mean (SD)	55.1 (19.6)	66.0 (12.2)
	Median (range)	60.0 (0.0-84.0)	68.0 (38.0-90.0)
<b>Age group</b>	≤16 years	11 (8.1%)	0 (0.0%)
	17-49 years	30 (22.2%)	18 (12.2%)
	50-64 years	42 (31.1%)	40 (27.2%)
	65-74 years	35 (25.9%)	53 (36.1%)
	≥75 years	17 (12.6%)	36 (24.5%)

The two pivotal clinical studies were designed according to the TGA adopted EU guideline and the US FDA as published in the Guidance for Industry; Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use (FDA, 1999b).<sup>7</sup>

## Pharmacology

Due to the nature of Evicel, no pharmacokinetic or pharmacodynamic studies have been conducted in man. Evicel is intended only for direct topical application onto the surface of tissue at the surgical site, where the product components interact with each other to initiate the last phase of physiological blood coagulation and form a fibrin clot. The product does not involve systemic interaction, and intravascular administration is contraindicated.

Pharmacokinetic studies in animals have been conducted and are addressed under *Nonclinical Findings* in this AusPAR.

## Efficacy

### Introduction

The sponsor conducted and presented two randomised controlled clinical trials studying patients who required additional haemostatic support during surgery. Between 2005 and 2006 a total of 141 patients received Evicel. Patients were randomised to receive either Evicel or a control treatment during retroperitoneal or abdominal surgery (study 400-05-06) or vascular surgery (400-05-01).

The sponsor also presented eight further studies as additional evidence of Evicel's safety and efficacy. One study was conducted in patients undergoing vascular surgery, three were conducted in patients undergoing liver surgery and four were conducted in patients undergoing orthopaedic surgery. These eight trials have been treated as supportive studies throughout this assessment as they used Evicel's precursor, Quixil. The sponsor stated that because of the overall comparability of the two products in respects other than the formulation with TA, the clinical data for Quixil provide support for the safety and efficacy of Evicel in other surgical settings.

The supportive studies were considerably older than the pivotal studies, as patients received Quixil between 1996 and 2002. These studies were also generally smaller than

the pivotal studies and ranged from 13 patients in one case series to 121 randomised patients in a comparative study (of which 58 received Quixil). Six of the eight studies were comparative, where the comparator groups varied and included Kaltostat (calcium/sodium alginate dressing), cauterisation with diathermy, suture ligation, Tissucol Kit R, and FDA-approved haemostatic agents (such as Avitene, Gelfoam, Oxycel, Surgicel, Surgicel Nu-Knit, Thrombinar, Actifoam).

In some studies Quixil patients received the same treatment as the control group, plus Quixil.

Two supportive studies were case series where all patients received Quixil, which provided very limited information on Quixil's relative efficacy (OFI-LIV-002-UK and OFI-THR-005-UK). These two studies have not been considered in the efficacy component of this report but have been included in the safety component.

Additional research indicates that the sponsor provided an additional randomised, comparative study of 121 patients undergoing liver surgery to the FDA in order to obtain FDA clearance for Evicel.<sup>9</sup> It is unclear why the sponsor did not present this as either a pivotal or supportive study in this submission.<sup>10</sup>

## **Main (pivotal) studies**

### ***Study 400-05-06***

#### *Objectives*

The objective of this study was to assess whether Evicel fibrin sealant was non-inferior to Surgicel (an oxidised, regenerated cellulose haemostat) in achieving haemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery.

The primary outcome was haemostatic efficacy, specifically the absence of bleeding at the Target Bleeding Site (TBS) at 10 minutes (min) following treatment randomisation, without using any additional haemostatic measures (other than the assigned Evicel or Surgicel). The study's hypothesis was that Evicel would be non-inferior to Surgicel in achieving haemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery. The study design was non-inferiority because an active comparator (Surgicel) was used.<sup>11</sup> Surgicel is TGA listed for use in surgical procedures to assist in the control of capillary, venous and small arterial bleeding, when ligation or other conventional methods of control are impractical or ineffective.

The sponsor cited an FDA guidance document for the safety and efficacy evaluation of fibrin sealant products (FDA, 1999) which indicates that both control of haemostasis within a specific time and time to haemostasis are appropriate primary endpoints.

#### *Study participants*

The study population included patients undergoing non-emergency retroperitoneal or intra-abdominal surgery procedures in whom surgeons intra-operatively identified a soft tissue target bleeding site (TBS) for which an adjunctive haemostat was indicated. Patients had to be willing to participate in the study and must have provided written informed consent. Surgical procedures included, but were not limited to:

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<sup>9</sup> FDA, Prescribing Information for Evicel, 2009. Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm114073.pdf>

<sup>10</sup> Sponsor comment: "In the CTD file of the version submitted to TGA, the study is included both in the summary section and as a full report."

<sup>11</sup> Sponsor comment: "The trial was an adaptive design where if certain conditions were met, the primary parameters were also tested for superiority".

- Urology: simple or radical nephrectomy; adrenalectomy (open); radical prostatectomy; pyeloplasty
- Gynaecology: radical hysterectomy; radical cystectomy (bladder removal); lymphadenectomy (lymph node dissection); primary tumour reduction surgery (ie ovarian cancer surgery)
- General surgery: colectomy with or without anal anastomoses; low anterior resections; abdominoperineal resections; retroperitoneal tumour resection surgery.

The study's exclusion criteria consisted of the following:

- Patients undergoing emergency surgery
- Patients with parenchymal or anastomotic bleeding sites (these were not considered for randomisation)
- Patients with any intra-operative findings identified by the surgeon that may have precluded conduct of the study procedure
- Patients with known intolerance to blood products or to one of the components of the study product
- Patients unwilling to receive blood products
- Patients with autoimmune immunodeficiency diseases (including HIV)
- Patients who were known, current alcohol and/or drug abusers
- Patients who had participated in another investigational drug or device research study within 30 days of enrolment
- Female patients who were pregnant or nursing

Upon enrolment, patients were stratified for age (16 years or less; over 16 years) to collect paediatric usage data.

#### *Treatments*

Prior to surgery, eligible patients provided written consent and participated in screening and baseline data collection. The surgical procedure was performed using the surgeon's standard surgical techniques. The TBS was the first site in the soft tissue identified with mild to moderate bleeding, where conventional methods of control (such as suture, ligature and cautery) were ineffective or impractical and an adjunct was required to achieve haemostasis. Upon intra-operative identification of the TBS the randomisation envelope was opened, the stopwatch was simultaneously started, and the allocated treatment was immediately administered.

Prior to randomisation both Evicel and Surgicel were prepared and made available in the operating theatre. Immediately after randomisation to the Evicel treatment group the product (2 x 5 mL) was applied. Evicel could be dripped or sprayed onto the TBS using the application device supplied, with each device for single use only. When dripping, the tip of the applicator was kept close to the tissue surface but without touching the tissue during application. When spraying, the distance between the nozzle and the tissue surface was 10 to 15 cm and the Evicel was sprayed in short bursts to form a thin even layer.

Immediately after randomisation to the Surgicel treatment group the product was applied to the TBS. Surgicel was supplied as 10.2 x 20.3 cm sheets, although it was unclear whether the entire sheet was applied. Surgicel was not lifted or disturbed when assessing haemostasis.

The quantities of Evicel or Surgicel supplied for each application were considered sufficient to achieve haemostasis at the TBS; however, additional amounts could be re-

applied according to the surgeon's discretion. For both treatment groups, assessment of bleeding was performed at 4, 7 and 10 minutes following randomisation. In the event of brisk bleeding during the 10 min observational period, or if haemostasis was not achieved by the end of this period, the surgeons could apply and record the use of further haemostatic measures.

#### *Outcomes/endpoints*

The primary outcome was haemostatic efficacy, defined as the absence of bleeding at the TBS at 10 min following treatment randomisation, without using any additional haemostatic measures. Secondary outcomes included:

- Haemostasis at the target bleeding site at 4 and 7 min following randomisation (subjects with additional haemostatic measures up to 10 min were considered failures).
- Absolute Time To Haemostasis (TTH)
- Incidence of treatment failure
- Incidence of potential bleeding related complications to end of follow up
- Safety variables, including coagulation parameters, full blood count, and adverse events.

Treatment failure was defined as either the presence of bleeding at the TBS 10 min following randomisation; or where brisk bleeding occurred, requiring administration of additional haemostatic measures, during the 10 min observation period.

The sponsor stated that assessment of haemostasis at defined time points is a direct method of evaluating the efficacy of a product designed to be an adjunct in achieving haemostasis following retroperitoneal and intra-abdominal surgical procedures. Surrogate endpoints were not required. The sponsor noted that measurement of haemostasis as an endpoint is also recommended by the FDA in their guidance document for the efficacy evaluation of fibrin sealant products and that regulatory agencies and the surgical community generally accept that a faster time to haemostasis is clinically beneficial. Additionally, recent Cochrane systematic reviews indicate that reduced perioperative bleeding can prevent blood transfusions and repeat surgery due to bleeding (Henry and Carless).<sup>12,13</sup>

#### *Statistical considerations*

For sample size determination, the sponsor assumed that the time to haemostatic success would be similar in retroperitoneal and intra-abdominal surgery and that 90% of patients in both the Evicel and Surgicel groups would achieve haemostatic success. Evicel treatment would be claimed non-inferior to Surgicel if the lower limit of the two-sided 95% confidence interval (CI) for the ratio of proportions of success was greater than 0.8. It was calculated that a sample size of 126 patients (63 per arm) was needed to achieve 95% confidence and 90% power. At least 10 patients aged 16 years or less were to be enrolled in the study. In order to account for patient dropouts, the sample size was increased to a final sample size of 130 patients (65 per arm) enrolled into the study.

No interim analyses were planned or undertaken, and no stopping rules were defined.

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<sup>12</sup> Henry DA, Carless PA, Moxey AJ et al. Antifibrinolytic use for minimising perioperative allogeneic blood transfusion (Review). Cochran Collaboration Issue 3, 2011.

<sup>13</sup> Henry DA, Carless PA, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *Can Med Assoc J* 2009; 180: 183-193.

Treatment was assigned randomly to each subject on a 1:1 basis. An independent statistician generated the randomisation code and each site was provided with envelopes, each bearing the subject randomisation number and containing the treatment allocation.

Randomisation was stratified within each participating centre.<sup>14</sup> At sites capable of enrolling both adult and paediatric subjects, subjects were stratified by age ( $\leq 16$ ,  $> 16$ ) and 2 sets of randomisation envelopes were provided to those sites.

The sponsor stated that due to the differences in application of Evicel and Surgicel, blinding of the surgeon and intra-operative outcome assessors was not feasible.

However to avoid bias in the conduct of the surgical procedure, randomisation only took place after:

- both Evicel and Surgicel had been prepared and made available in the operating room,
- the surgical procedure had been performed according to the institution's standard of care,
- the surgeon had encountered a region or site<sup>15</sup> with soft tissue retroperitoneal bleeding or intra-abdominal bleeding and made attempts to control bleeding by conventional surgical techniques,
- the surgeon confirmed that control of bleeding by conventional surgical techniques was ineffective or impractical.

It would have been feasible to blind study patients, laboratory investigators and outcome assessors reporting upon postoperative adverse events to treatment group; however, it was not reported that this took place.

All analyses were produced using SAS and a 5% level of significance was used for any statistical tests ( $p < 0.05$ ). The primary analysis variable was haemostasis outcome at 10 min. Analysis using the "intention to treat" (ITT) patients (all randomised patients) was considered to be primary. Analysis using the "per protocol" (PP) analysis set (all subjects in the ITT who had no major protocol violations) was to be confirmatory.

The relative risk for achieving haemostatic success, including its 2-sided 95% confidence interval (CI), was calculated using the method described by Koopman. When the lower limit of the 95% CI was above 0.8, non-inferiority of Evicel compared with Surgicel for haemostatic success was assumed. When the lower limit of the 95% CI was above 1, superiority of Evicel compared with Surgicel was concluded, and the p-value was calculated.

Independent FDA analysis of the statistical analysis plan suggests that the statistical analysis plan was acceptable.<sup>16</sup>

For the primary analysis, missing data were considered failures. Sensitivity analyses were planned to assess the impact of missing data on the primary analysis. These included considering missing data as successes and also a worst case scenario; where missing data for the Evicel patients were considered failures and missing data for the Surgicel group were considered successes.

No statistical analysis of safety outcomes was performed. Instead, adverse event data were summarised descriptively using frequencies and associated percentages and using Medical

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<sup>14</sup> Sponsor comment: "Stratification was by age and not by study centre."

<sup>15</sup> Sponsor comment: "It had to be the *first* bleeding site encountered to avoid bias and that was declared in all the reports."

<sup>16</sup> FDA, Statistical Evaluation and Review – Evicel, 2008. Available at: <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductSBLAs/FractionatedPlasmaProducts/ucm114085.htm>

Dictionary for Regulatory Activities (MedDRA) coding. Exploratory p-values were calculated for adverse events using the chi-squared test. This is an acceptable statistical approach.

For the primary analysis, additional subgroup analyses according to age were performed. These included an adult analysis set (patients aged more than 16 years to less than 65 years), a paediatric analysis set (patients aged 16 years or less); and an adult 65+ analysis set (patients aged 65 years or more).

An exploratory analysis using a logistic model was planned in the ITT set to assess the effect of centre, centre by treatment interaction and age ( $\leq 16$  versus  $>16$  to  $<65$ ,  $\geq 65$ ). In the event that more than 4 subjects were randomised to one treatment but received the other, an exploratory analysis was planned to assess this effect based on the treatment received. TTH was recorded using actual time for an exploratory survival analysis.

## Results

### Participant flow

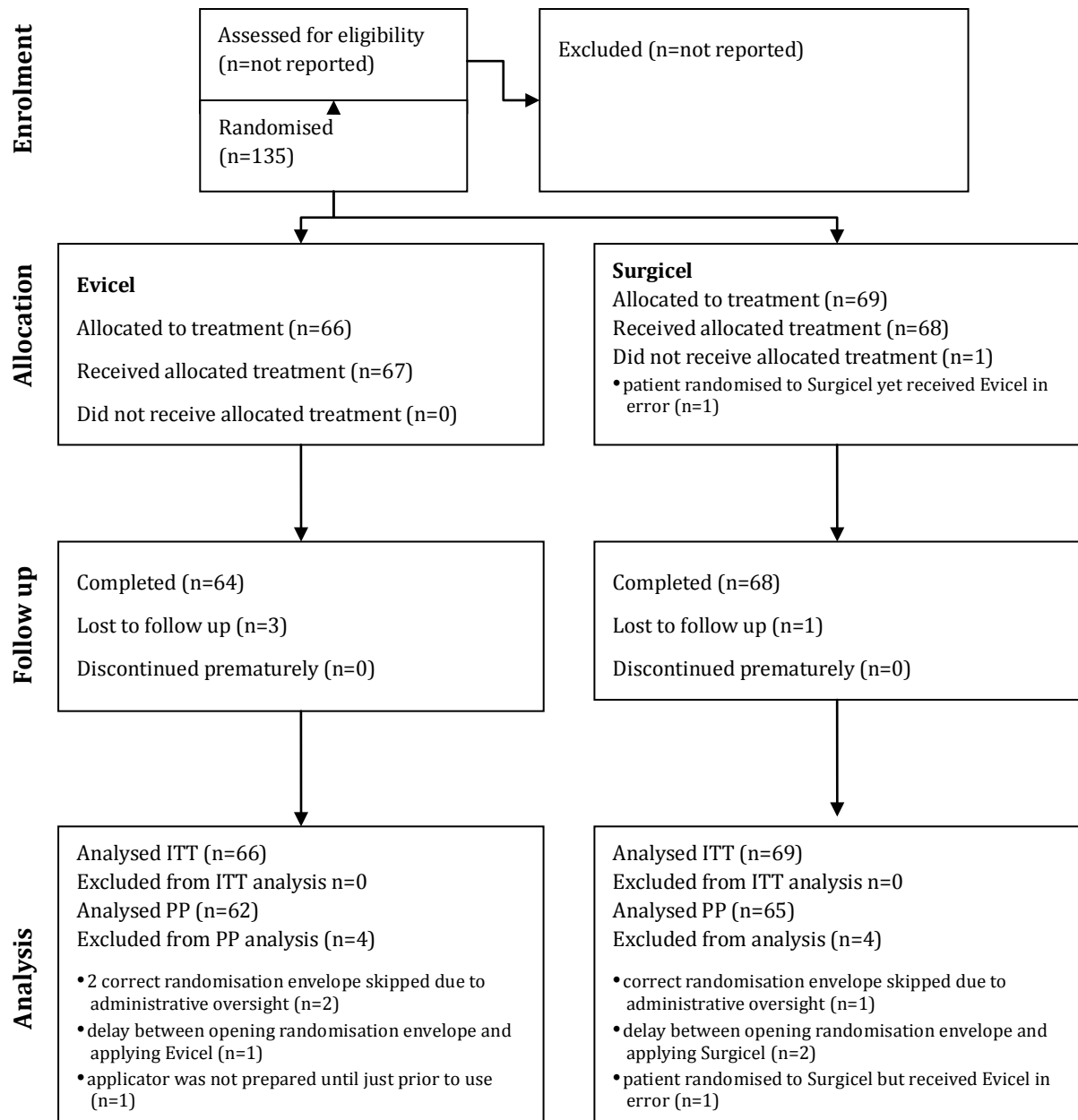
Participant flow is shown in Figure 1.

Three Evicel patients were lost to follow up. One patient died eight days postoperatively; one patient was unable to be reached by phone; and one patient had limited follow up. One Surgicel patient was lost to follow up, although no reason was provided.

For the primary effectiveness variable (haemostasis at 10 min) the length of follow up was 10 min following randomisation. For the secondary effectiveness outcomes various follow up periods were defined, including haemostasis at the TBS at 4 and 7 min following randomisation; absolute time to haemostasis (TTH); and safety outcomes to  $>7$  to 14 days post surgery. However, no dates were provided for safety follow up.

A total of 124 deviations affected 37 Evicel patients and 50 Surgicel patients. Generally these were procedural, such as follow up visits or laboratory parameters which occurred outside of the protocol schedule, although deviations related to the randomisation process were also encountered. A major deviation was defined as one affecting the primary parameter. Eight major deviations resulted in exclusions of patients from the PP analysis set (5 Evicel patients and 3 Surgicel patients).

Re-application of the randomised treatment within the 10 min observation period was permitted where necessary, at the surgeon's discretion. If haemostasis had not been achieved at the end of the 10 min observation period, the study surgeon could use any other topical haemostat (excluding other fibrin sealants) at the TBS, and record the patient as a treatment failure. Any brisk bleeding during the 10 min observation period could be treated with additional haemostatic measures and recorded as a treatment failure. The details of all topical haemostatic agents used throughout the procedure were recorded. ~~Why parents don't do this on their own, parents are encouraged to continue their participation in the study at~~



### Recruitment

Recruitment took place between 28 February 2006 and 27 December 2006. The study was conducted at 17 participating centres in the US, of which 16 enrolled between one and twenty treated patients. Four centres recruited three or less patients, while two centres recruited 20 patients each.

### Conduct of the study

No amendments to the protocol were issued during the study. Although abnormal laboratory parameters were to be recorded as adverse events, these were limited to those only abnormal laboratory parameters that were considered by the investigator to be clinically significant.

The sponsor indicated that a number of quality assurance audits were carried out, as well as routine monitoring of each investigational site. Other than the major and minor deviations described above, the sponsor did not report any other findings of the quality assurance audits.



### *Baseline data*

The sponsor stated that following randomisation, the treatment groups were well matched in demographic characteristics. Statistical analysis of the demographic data was not provided.

The mean age of the Evicel group was higher than of the Surgicel group (57.3 versus 53 years). The Surgicel group contained more paediatric patients than the Evicel group (7 versus 4, respectively). The Evicel group contained a higher proportion of male patients than the Surgicel group (45.5% versus 39.1%). Evicel patients were heavier than Surgicel patients (body mass index [BMI] 29.9 versus 27.7), and more patients in the Surgicel group had a history of smoking (49.3% versus 45.5%). In both groups, urology was the most represented surgery specialty (41.8% Evicel and 36.8% Surgicel). Initial attempts to achieve haemostasis at the TBS were made using cautery in most cases (50.7% for Evicel and 72.1% for Surgicel). Sutures were used in 14.7% of Surgicel patients and 16.4% of Evicel patients, and ligation was used in 7.4% of Surgicel patients and 4.5% of Evicel patients. However, in 32.8% of Evicel subjects and 19.1% of Surgicel subjects none of these conventional methods were used.

Bleeding at the TBS was mild for 61.2% of Evicel patients and for 52.9% of Surgicel subjects, and in the remainder of cases bleeding was moderate.

An imbalance in paediatric patients was noted across the treatment groups (four Evicel, seven Surgicel). This was due to low recruitment within centres and skipped randomisation numbers in two of the centres.

The number of product re-application was similar in both treatment groups. One Surgicel patient received heparin. No Evicel patients received heparin.

With the exception of one patient, all patients received the treatment they had been randomised to (one patient was randomised to Surgicel but received Evicel in error).

The study employed broad inclusion criteria and a variety of surgical specialties was assessed. Evicel's intended indication is as a supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. This was satisfactorily reflected in the study's patient population, where haemostasis was generally attempted by the surgeon using conventional means (such as cautery) prior to applying Evicel. Evicel is also indicated for suture support for haemostasis in vascular surgery; however, this population was not assessed in this study. A separate study (400-05-01) was conducted to assess this indication.

### *Numbers analysed*

Both the primary and secondary efficacy outcomes were analysed by ITT and also using PP analysis. For the Evicel group there were 66 patients in the ITT set and 62 in the PP set. For the Surgicel group there were 69 patients in the ITT set and 65 in the PP set.

### *Outcomes and estimation*

The primary efficacy endpoint was haemostasis at 10 min. More patients in the Evicel group (63/66, 95.5%) achieved haemostasis at 10 min compared with the Surgicel group (56/69, 81.2%) (relative risk [RR] 1.18 [95% CI 1.04, 1.36]) (p<0.05).

The relative proportions of haemostatic success at 4 and 7 min were consistent with the haemostatic outcome at 10 min (Table 4).

**Table 4: Haemostatic success at 4 and 7 minutes post randomisation**

Outcome	Evicel	Surgicel	Statistical summary
Haemostasis at 4 minutes	50/66 (75.8%)	37/69 (53.6%)	RR 1.41 (1.10, 1.86) p<0.05
Haemostasis at 7 minutes	60/66 (90.9%)	53/69 (76.8%)	RR 1.18 (1.02, 1.40) p<0.05

Time to haemostasis was lower in the Evicel group (range 0.3 to 8.1 minutes, median 2.3) than in the Surgicel group (0.8 to 9.8 minutes, median 3.4) (p<0.001).

Further evaluation of TTH by TBS severity showed that the success rates were better in the mild bleeding group (100% for Evicel and 89.2% for Surgicel) compared to the moderate bleeding group (88.5% for Evicel and 71.9% for Surgicel).

The incidence of treatment failure (failure to achieve haemostasis at 10 min or the need to administer additional haemostatic measures during the 10 min observation period) was higher in the Surgicel group than the Evicel group (Table 5).

**Table 5: Incidence of treatment failure**

	Evicel group	Surgicel group	Statistical summary
<b>Other haemostatic measures required</b>	0 (0.0%)	4/69 (5.8%)	p=0.05
<b>Presence of bleeding at 10 minutes</b>	3 (4.5%)	9/69 (13%)	RR 0.35 (1.10, 1.13)
<b>Overall incidence of treatment failure (either of the above)</b>	3 (4.5%)	13 (18.8%)	NR

NR: not reported

Four failures were due to brisk bleeding at the TB, and occurred exclusively in Surgicel subjects (2 adult and 2 paediatric patients) (p=0.05 versus Evicel patients).

The findings of a benefit of Evicel are clinically as well as statistically relevant because it is widely accepted in the surgical community that reducing bleeding time in surgery, and with it reduced blood loss, is better for patients.

Surgicel patients had a longer postoperative length of stay (mean 9.9 days) than Evicel patients (mean 7 days), although 6 patients (3 per treatment group) did not have discharge dates recorded. No statistical analysis was performed.

#### *Ancillary analyses*

Subgroup analyses for the adult, adult 65+ and paediatric age groups were performed. These all found that more Evicel than Surgicel patients achieved haemostasis at 4, 7 and 10 min. No statistical differences were reported.

Regarding TTH:

- in adult patients, Evicel patients ranged from 0.4 to 8.1 min (median 2.8) while Surgicel patients ranged from 1.0 to 7.8 min (median 3.1).

- in adult patients 65+, Evicel patients ranged from 0.3 to 7.5 min (median 2.3) while Surgicel patients ranged from 0.8 to 9.8 min (median 4.0).
- in paediatric patients, Evicel patients ranged from 0.7 to 3.0 min (median 1.7) while Surgicel patients ranged from 1.4 to 6.5 min (median 3.2).

### ***Study 400-05-01***

#### *Objectives*

The primary study objective was to evaluate whether Evicel reduced time to haemostasis (TTH) during vascular surgical procedures on an end-to-side femoral or upper extremity arterial anastomosis utilising uncoated or heparin coated polytetrafluorethylene (PTFE) compared to manual compression (MC). The primary endpoint was haemostatic efficacy, specifically the absence of bleeding at the study anastomotic site (SAS) 4 min after randomisation to treatment.

The study aimed to test the null hypothesis that the proportion of bleeding at 4 min (yes/no) for the subjects receiving Evicel was the same as for those using MC (that is, Evicel = MC) versus the alternate hypothesis that the proportion of bleeding in the two treatment groups differed (that is, Evicel  $\neq$  MC).

The sponsor indicated that measurement of haemostasis as an endpoint is recommended by the FDA in their guidance document for the efficacy evaluation of fibrin sealant products. The study analysed the proportion of success at defined time points, rather than recording absolute values of time to haemostasis, so as to maintain minimal disruption to the haemostatic process in the MC group. The sponsor also indicated that this method is recognised as satisfactory by FDA and other regulatory authorities.

#### *Study participants*

Included in the study were male and female subjects, 18 years of age or older, requiring elective, primary or repeat vascular procedures with at least one end-to-side femoral or upper extremity vascular access arterial anastomosis (for example, femoral-femoral, femoral-popliteal, femoral-tibial, ilio-femoral, aorto-bifemoral, abdominal aortic aneurysm, upper extremity vascular access for dialysis) using uncoated or heparin coated PTFE grafts and polypropylene sutures (size 5-0 or 6-0) with a 1:1 needle-to-thread ratio. Subjects were included if, following initial arterial clamp release, the study surgeon determined that adjunctive measures were needed to obtain haemostasis at the SAS. Subjects had to be willing and capable of participating in the study and must have provided written, informed consent.

The study exclusion criteria consisted of the following:

- Subjects undergoing re-vascularisation using autologous conduits (for example, saphenous vein) or prosthetic material other than uncoated or heparin coated PTFE
- Subjects undergoing emergency surgery
- Subjects with any intra-operative findings that precluded conduct of the study procedure
- Subjects with known intolerance to heparin, blood products or to one of the components of the study product
- Subjects unwilling to receive blood products
- Subjects with autoimmune immunodeficiency diseases (including known human immunodeficiency virus [HIV])
- Subjects who were known, current alcohol and/or drug abusers

- Subjects who had participated in another investigational drug or device research study within 30 days of enrolment
- Female subjects who were pregnant or nursing

### *Treatments*

Prior to surgery, eligible subjects provided written consent and participated in screening and baseline data collection. The surgical procedure was carried out using the surgeon's standard surgical techniques, with subjects receiving heparin before arterial clamping. The SAS was the femoral or upper extremity artery anastomosis. Subjects were to be randomised once suturing at the SAS was complete, arterial clamps were released and the surgeon considered the suture line to be secure. Randomisation only took place if, after securing the suture line, there remained a presence of bleeding which the surgeons determined required adjunctive haemostatic measures. In these cases, the arterial clamps were reapplied and randomisation to Evicel or MC took place. Both treatments were made available in the operating theatre before randomisation.

Prior to randomisation, Evicel was prepared in the application device, ready for administration. Immediately after randomisation to the Evicel treatment group, the surgeon was recommended to apply the total volume of pre-prepared product (2 mL each component) by dripping onto the SAS. The tip of the applicator was kept close to the tissue surface but without touching the tissue during application. In this study, dripping of the product was recommended but not spraying. Arterial clamps were removed one minute following end of product application, in order to allow time for the fibrin sealant to set.

After randomisation to the MC treatment group, arterial clamps were removed immediately and MC applied to the SAS. MC comprised light manual pressure with sponges. At the specific time points for assessing haemostasis, one corner of the sponge was cautiously lifted and, if no bleeding was observed, it was carefully removed from the surface of the SAS. If bleeding was observed the sponge was immediately replaced.

For both the Evicel and MC groups, assessment of bleeding was performed at 4, 7 and 10 min following randomisation. When haemostasis was achieved prior to the end of the 10 min observational period the surgeon was to prepare to close the surgical wound immediately. In the event of brisk bleeding during the 10 min observational period or if haemostasis was not achieved by the end of this period, the surgeons could apply and record the use of further haemostatic measures.

### *Outcomes/endpoints*

The primary endpoint was haemostatic efficacy, which was defined as the absence of bleeding at the SAS 4 min following randomisation to treatment.

Secondary endpoints included:

- Absence of bleeding at the SAS 7 and 10 min following randomisation
- Incidence of treatment failure.
- Incidence of potential bleeding related complications up to 5 week follow up
- Adverse events up to 5 week follow up.

Treatment failure was defined as the presence of bleeding at the SAS at 10 min or the need to administer additional haemostatic measures during the 10 min observation period.

The sponsor stated that assessment of haemostasis at defined time points is a direct method of evaluating the efficacy of a product designed to be an adjunct in achieving haemostasis following vascular surgical procedures. Surrogate endpoints were not required.

The sponsor also noted that measurement of haemostasis as an endpoint is recommended by the FDA in their guidance document for the efficacy evaluation of fibrin sealant products and stated that regulatory agencies and the surgical community generally accept that a faster time to haemostasis is clinically beneficial. The clinical evaluator agreed that this is valid.

#### *Statistical considerations*

For sample size determination, the sponsor assumed that the success rate in the MC group would be 0.35 and in the Evicel group would be 0.63, based on data from a similar study. In the previous study the active treatment control group (thrombin soaked gelatine sponge) had a success rate of 0.40 but it was expected that in the current study the response in the MC group would be lower. It was calculated that with a significance level of 0.05, a sample size of 144 (72 subjects per arm) would be required to achieve 90% power to detect a difference of 0.28 between the null hypothesis that both treatment and control proportions were 0.35 and the alternative hypothesis that the proportion in the treatment group was 0.63, using a two-sided Chi-square test. In order to account for subject dropouts, the sample size was increased to a final sample size of 150 (75 per arm) enrolled into the study. An additional 6 subjects were to be recruited to allow for withdrawals and was considered adequate because the time to the primary endpoint was very short.

No interim analyses were planned or undertaken.

Treatment was assigned randomly to each subject on a 1:1 basis. Computer generated randomisation schedules of treatment group assignment were provided which were placed in sealed envelopes.

Randomisation was stratified within each participating site and also stratified for femoral versus upper extremity procedures. Each site was provided with a series of randomisation envelopes, each bearing the subject randomisation number and artery type on the outside. The appropriate envelope was sent to the operating room with other study materials, and had to be opened to reveal the treatment allocation. If the subject was not randomised, the unused envelope was returned to the series and used for the next subject with the same artery type.

The sponsor stated that given the differences in application of Evicel and MC it was not possible for the surgeon to be blinded to treatment. However, to avoid bias in the conduct of the surgical procedure, randomisation only took place after preparation of Evicel in the application device for every subject, completion of the SAS, release of arterial clamps and placement of additional sutures as needed until the surgeon deemed that the suture line was secure and determination by the surgeon that adjunctive measures were needed to obtain haemostasis at the SAS. While it was not feasible to blind intra-operative assessors, the study subjects and postoperative assessors could have been blinded but it was not reported that this took place.

The primary effectiveness variable was the absence of bleeding at SAS 4 min following randomisation. Analysis using the "full analysis" set (FAS) (all randomised subjects, equivalent to the ITT set) was considered to be primary, while analysis using the per protocol (PP) analysis set (all subjects in the FAS who had no major protocol violations) was to be confirmatory. Absence of bleeding at SAS 4, 7 and 10 min following randomisation, incidence of treatment failures and incidence of potential bleeding related complications were analysed using a logistic model (with treatment, centre, and artery type in the model). For the primary endpoint, a significant treatment p-value (<0.05) would allow the acceptance of the alternative hypothesis, indicating a statistically significant treatment difference. The logistic models employed were not detailed; thus it is unclear whether these analyses were acceptable.

If the logistic model fit was 'questionable' as reported in the output provided by the analysis program, then an additional analysis was to be carried out in which centres would be pooled or removed from the model. This analysis would be considered exploratory. The exploratory models employed were not detailed; thus it is unclear whether these analyses were acceptable.

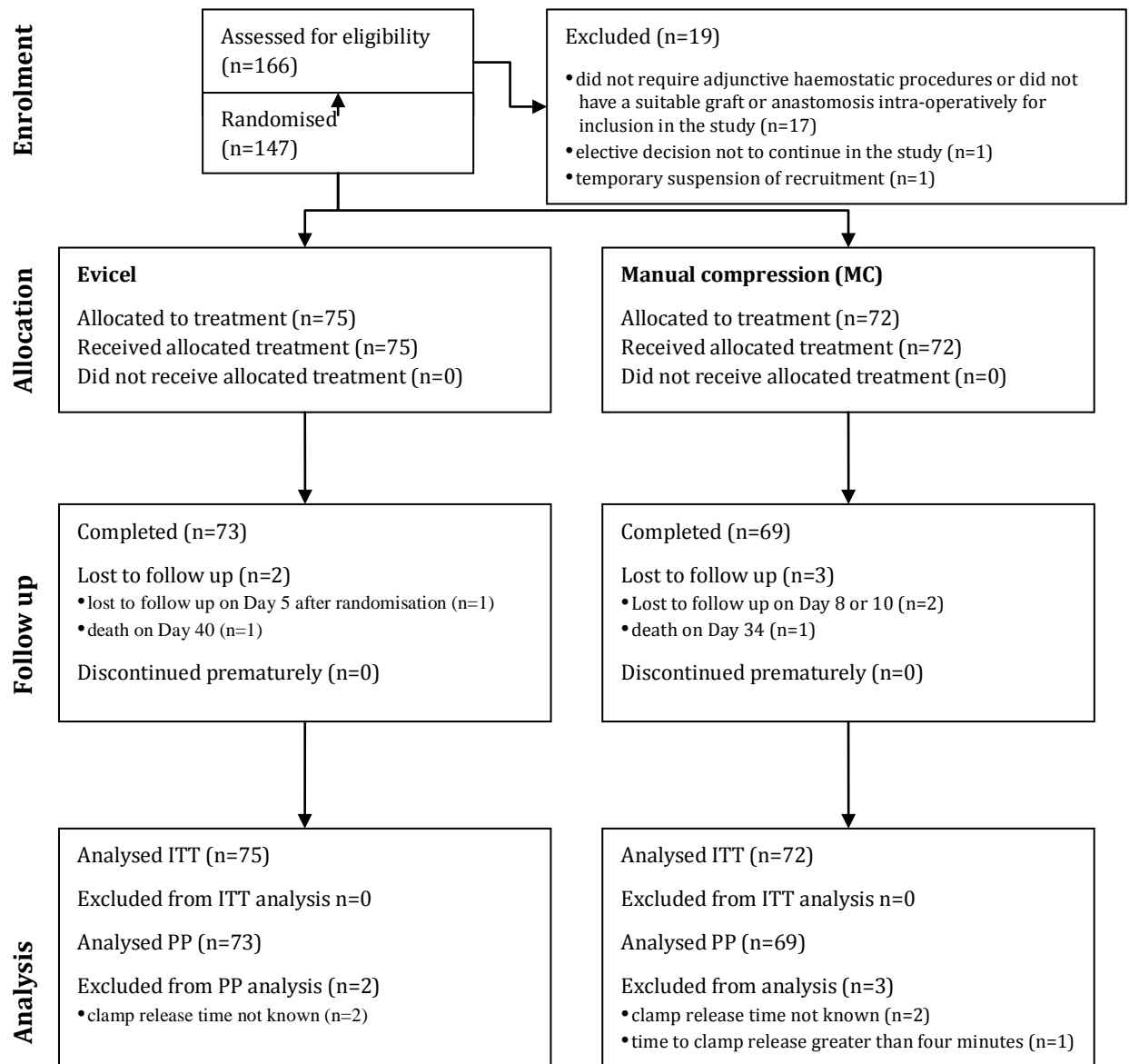
Since there was an imbalance between centre and artery type, an additional model was fitted which excluded centre from the analysis. This was an alternative to pooling centres that had recruited a small number of patients, as this failed to correct the imbalance unless a large number of centres were pooled. This model was presented as the 'revised model' in the results and removed the effect of centre on the analysis. This model appears appropriate, as effects of centre were shown to not be statistically significant ( $p=0.945$ ), and the revised model had the same overall findings as the original model. A 'worst case' analysis was also carried out which assumed that, for five patients excluded from the PP set due to questionable clamp release times, the time to haemostasis was missing. For this analysis the two subjects in the Evicel group were considered failures and the three subjects in the MC group were considered successes.

Since neither centre nor artery type affected haemostasis at 4 min an additional chi-square test (which just considered treatment) was carried out for the primary endpoint (FAS) only. This allowed reporting of relative risks.

### *Results*

#### Participant flow

Participant flow is shown in Figure 2.

**Figure 1: 400-05-01 Participant flow**

Two Evicel patients were lost to follow up due to death at 5 and 40 days postoperatively. Three MC patients were lost to follow up. One patient died at Day 34 postoperatively and no details were given regarding the two remaining patients.

For the primary effectiveness variable (haemostasis at 4 min) the length of follow up was 4 min following randomisation.

The overall length of follow up was five weeks; however, no dates were provided.

There were only five major protocol deviations and the five patients involved were excluded from the PP analysis set. For four patients (two in the Evicel group, two in the MC group) the time of clamp release was unknown and in one patient (in the MC group) clamp release occurred more than four minutes after randomisation.

All patients received the correct study treatment as randomised; however, some deviations in the randomisation protocol occurred (in one patient the Evicel vial was not prepared prior to randomisation and in four centres randomisation envelopes were occasionally taken out of sequence). The sponsors stated that all out of sequence randomisation appeared to be circumstantial or due to genuine human error. The deviations were considered and accounted for in the analysis of results.

### *Recruitment*

Recruitment took place from 9 June 2005 to 3 March 2006. The planned recruiting sites consisted of five centres in the UK and 13 centres in the US. Actual recruitment took place in four UK and 12 US centres only, as one centre in the UK and one in the US was closed early as no patients were recruited to the study within 4 months of centre initiation.

### *Baseline data*

The mean age of the Evicel group (n=75) was 66.0 years (standard deviation [SD] 10.6), and for the MC (n=72) was 66.0 years (SD 13.7). There were 41 males and 34 females in the Evicel group and 36 males and 36 females in the MC group. Mean BMI (kg/m<sup>2</sup>) in the Evicel group was 27.9 (SD 6.5) and 26.9 (SD 6.8) in the MC group. In the Evicel group, 15 subjects (20.0%) never smoked, 39 (52.0%) were ex-smokers and 21 (28.0%) were current smokers. In the MC group, 16 participants (22.2%) never smoked, 35 (48.6%) were ex-smokers and 21 (29.2%) were current smokers. Forty seven participants (62.7%) in the Evicel group and 47 (65.3%) in the MC group had peripheral vascular disease, 28 participants (37.3%) in the Evicel group and 24 (33.3%) in the MC group had renal disease, 59 participants (78.7%) in the Evicel group and 57 (79.2%) in the MC group had hypertension and 32 participants (42.7%) in the Evicel group and 39 (54.2%) in the MC group had coronary artery disease. Type 1 diabetes was present in 6 participants (8.0%) in the Evicel group and 3 (4.2%) in the MC group, while Type 2 diabetes was present in 26 participants (34.7%) in the Evicel group and 24 (33.3%) in the MC group. The sponsors stated that the treatment groups were similar in demographic characteristics, although statistical analysis was not reported.

For the Evicel group, the surgical procedures consisted of 48 (64.0%) femoral procedures and 27 (36.0%) upper extremity procedures. For the MC group there were 51 (70.8%) femoral procedures and 21 (29.2%) upper extremity procedures. Mean operation duration was 134.6 min (SD 71.2) in the Evicel group and 138.9 min (SD 66.5) in the MC group. The mean total heparin dose (international units [IU]) was 5100.0 (SD 2036.8) in the Evicel group and 5035 (SD 2237.5) in the MC group. Polypropylene sutures were used in all patients in both groups and all patients except one in the Evicel group had uncoated PTFE grafts.

Evicel's intended indication is for suture support for haemostasis in vascular surgery. This was satisfactorily reflected in the study's patient population where patients received Evicel for suture support after undergoing a variety of vascular surgical procedures.

The sponsors stated that following randomisation, the treatment groups were similar in demographic characteristics. Statistical analysis of the demographic data was not provided.

All patients received the treatment that they were randomised to. The majority of the 75 patients who were randomised to Evicel received all 4 mL of the product as planned in the protocol; however, 17 patients received less than 4 mL, with the unused amount ranging from 0.2 to 3.0 mL.

### *Numbers analysed*

For the Evicel group, there were 75 participants in the FAS and 73 in the PP set. For the MC group, there were 72 participants in the FAS and 69 in the PP set.

The efficacy outcomes were analysed using ITT (termed FAS by the sponsor) and also using PP.

### *Outcomes and estimation*

The primary outcome was haemostasis at 4 min. More patients in the Evicel group achieved haemostasis at 4 min compared with the MC group. This finding was confirmed by all analysis types (FAS original model, FAS revised model, FAS worst case model, PP



original model, PP revised model), as shown in Table 6. The effects of centre ( $p=0.945$ ) and artery type ( $p=0.729$ ) were not statistically significant.

**Table 6: Haemostasis at 4 minutes post randomisation**

Analysis model	Evicel group	MC group	Statistical summary
FAS original model	64/75 (85.3%)	28/72 (38.9%)	OR 11.3; 95% CI 4.7 – 27.5; $p<0.001$
FAS revised model	64/75 (85.3%)	28/72 (38.9%)	OR 9.1; 95% CI 4.1 – 20.1; $p<0.001$
FAS worst case model	62/75 (82.7%)	30/72 (41.7%)	OR 7.9; 95% CI 3.4 – 18.2; $p<0.001$
PP original model	62/73 (84.9%)	27/69 (39.1%)	OR 10.6; 95% CI 4.3 – 25.8; $p<0.001$
PP revised model	62/73 (84.9%)	27/69 (39.1%)	OR 8.7; 95% CI 3.9 – 19.4; $p<0.001$

CI – confidence interval; OR – odds ratio

For secondary outcomes, more patients in the Evicel group achieved haemostasis at 7 and 10 min compared with the MC group. Using the FAS, at 7 min 68/75 participants (90.7%) in the Evicel group and 43/72 (59.7%) in the MC group had achieved homeostasis (odds ratio (OR) for original model 7.9; 95% CI 2.8 – 21.9;  $p<0.001$ ; OR for revised model 6.5; 95% CI 2.6 – 16.1;  $p<0.001$ ). Again using the FAS, haemostasis at 10 min was achieved in 72/75 participants (96.0%) in the Evicel group and 50/72 (69.4%) in the MC group (OR for original model 18.5; 95% CI 3.7 – 91.8;  $p<0.001$ ; OR for revised model 10.9; 95% CI 3.1 – 38.8;  $p<0.001$ ).

There was no significant difference in the incidence of potential bleeding related complications between the two groups, with 12/75 experiencing complications (16.0%) in the Evicel group and 15/72 experiencing complications (20.8%) in the MC group (OR 1.5; 95% CI 0.6 – 3.7;  $p=0.426$ ). Complications included anaemia/ low haemoglobin/ low haematocrit (5 Evicel, 9 MC), haematoma (5 Evicel, 5 MC), bleeding (2 Evicel, 2 MC), increased sanguinous drainage (2 Evicel, 0 MC), seroma (0 Evicel, 1 MC), and ecchymosis (0 Evicel, 1 MC).

The incidence of treatment failure (the presence of bleeding at the SAS at 10 min or the need to administer additional haemostatic measures during the 10 min observation period) was higher in the MC group than the Evicel group. This was mainly due to the persistence of bleeding at the end of the 10 min observation period in more patients in the MC group (Table 7).

**Table 7: Incidence of treatment failure**

	Evicel group	MC group	Statistical summary
Other haemostatic measures required	3/75 (4.0%)	5/72 (6.9%)	NR
Presence of bleeding at 10 min	3/75 (4.0%)	22/72 (30.6%)	NR
Overall incidence of treatment failure (either of the above)	6/75 (8.0%)	23/72 (31.9%)	OR for original model 0.14; 95% CI 0.05 – 0.45; p<0.001; OR for revised model 0.18; 95% CI 0.07 – 0.48; p<0.001

NR: not reported

It should be noted that in both groups there is a discrepancy between the percentage of patients recorded as having treatment success (haemostasis at 10 min) and the percentage recorded as a treatment failure. For example, for the Evicel group the percentage of success at 10 min was 96%, while the percentage of treatment failure was 8%. The three Evicel subjects who required other haemostatic measures were included by the sponsor as treatment successes, which could be misleading.

The sponsor stated that the findings of a benefit of Evicel are clinically as well as statistically relevant because it is widely accepted in the surgical community that reducing bleeding time in vascular surgery is better for patients. The clinical evaluator advised that additionally, a reduction in blood loss is clinically relevant and important.

Evicel did not appear to lead to a reduced length of stay compared with MC (Evicel mean 5.1±8.1 days and MC mean 5.5±6.2 days). No statistical analysis was performed.

#### *Ancillary analyses*

In Study 400-05-01 all patients received heparin. Patients undergoing femoral procedures received approximately 70 IU/kg and patients undergoing upper extremity artery procedures received approximately 35 IU/kg. Of the Evicel patients (n=75), 48 had femoral procedures and 27 had upper extremity artery procedures. Of the MC patients (n=72), 51 had femoral procedures and 21 had upper extremity artery procedures.

In Evicel patients the dosage of heparin did not appear to compromise haemostasis at 4 min. In MC patients, a higher proportion (43%) of patients who received 35 IU/kg achieved haemostatic success at 4 min compared with patients who received 70 IU/kg (37%) but no statistical analysis was provided.

#### **Clinical studies in special populations**

Special studies in children, the elderly and patients with renal or hepatic impairment were not conducted. One pivotal study (400-05-06) performed subgroup analyses in children <16 years and in adults aged 65+. Regardless of age, haemostatic success with Evicel measured between 90% and 100% yet with Surgicel measured between 71% and 86%. The low numbers in the paediatric group make definitive conclusions difficult (Table 8).

**Table 8: Efficacy outcomes in special populations in patients undergoing retroperitoneal or intra-abdominal surgery**

Outcome	Evicel	Surgicel
<i>Adult aged 65+ (Evicel n=30, Surgicel n=22)</i>		
Haemostasis at 10 min	27 (90%)	19 (86.4%)
Mean time to haemostasis (min)	2.9±2.3	3.9±2.1
<i>Paediatric &lt;16 years (Evicel n=4, Surgicel n=7)</i>		
Haemostasis at 10 min	4 (100%)	5 (71.4%)
Mean time to haemostasis (min)	1.8±1.0	4.0±2.2
<i>ITT analysis: all patients (Evicel n=66, Surgicel n=69)</i>		
Haemostasis at 10 min	63 (95.5%)	56 (81.2%)
Mean time to haemostasis (min)	2.8±2.0	3.7±2.0

Adults aged 65+ had a longer TTH than the ITT analysis and haemostatic success at 10 minutes was lower. Paediatric patients achieved haemostasis more quickly and with more success than the ITT analysis. However, no statistical analyses on these sub-populations were performed and the limited number of patients studied restricts the applicability of the outcomes measured.

In Study 400-05-01, 89 of the 147 patients were aged over 64; however, no sub-group analysis of this population was performed.

## Supportive studies

### *Vascular surgery*

In a supportive study the primary efficacy outcome was TTH (Table 9), thus permitting broad comparison with the efficacy outcomes measured in the Evicel pivotal studies. This small comparative study found that patients treated with Quixil achieved haemostasis in a significantly shorter time than patients treated with control haemostatic measures. This is supportive of the outcomes seen in the pivotal studies.

**Table 9: Time to haemostasis in vascular surgery patients**

Study ID	n Quixil / n control	Comparator	TTH Quixil (mean min)	TTH control (mean min)	Difference
Q-CVS-015-UK	10/10	Kaltostat	1.6 (range 0-3)	19.6 (range 6-58)	p=0.0015

### *Liver surgery*

Two comparative studies assessed the efficacy of Quixil in patients undergoing liver surgery (Q-LIV-008-US and OFI-LIV-003 B). In one study the primary efficacy outcome was TTH (Table 10), thus permitting broad comparison with Evicel efficacy outcomes. This study found that patients treated with Quixil achieved haemostasis in a significantly shorter time than patients treated with control haemostatic measures. This is supportive of the outcomes seen in the pivotal Evicel studies.

**Table 10: Time to haemostasis**

Study ID	n Quixil / n control	Comparator	TTH Quixil (mean min)	TTH control (mean min)	Difference
Q-LIV-008 US	58/63	Avitene, Gelfoam, Oxycel, Surgicel, Surgicel Nu-Knit, Thrombinar, Actifoam	5.3 (range 2-41)	7.7 (range 2-26)	p=0.011 (one-sided) p=0.022 (two-sided)

In the remaining supporting study the primary efficacy outcome was intra-operative blood loss (mL) and this outcome is not directly comparable to Evicel studies. This small comparative study found no significant difference in intra-operative blood loss between treatment groups in liver surgery.

### ***Orthopaedic surgery***

Three comparative studies assessed the efficacy of Quixil in patients undergoing orthopaedic surgery (Q-THR-009-US, OFI-TKR-001-IL, and OFI-TKR-004-US). In each study the primary efficacy outcome was blood loss (mL) (Table 11), hence these results are not directly comparable to the pivotal Evicel studies. In all three studies patients treated with Quixil lost significantly less blood than patients treated with control haemostatic measures.

**Table 11: Blood loss in patients undergoing orthopaedic surgery**

Study ID; surgical procedure	n Quixil / n control	Blood loss Quixil (mean mL)	Blood loss control (mean mL)	Difference
<i>Total blood loss</i>				
Q-THR-009-US; orthopaedic surgery	38/43	698.7 (SD 337.96)	836.6 (SD 327.19)	p=0.0071 (one-sided); p=0.0141 (two-sided)
OFI-TKR-001-IL; orthopaedic surgery	29/30	473±297	1147±516	p<0.001
<i>Postoperative blood loss</i>				
OFI-TKR-004-US; orthopaedic surgery	25/28	185.9±133.4	452.3±298.0	p<0.001

### Evaluator's overall conclusions on clinical efficacy

The two pivotal clinical studies were designed according to the TGA adopted EU guideline and the US FDA.<sup>17,18</sup> Both studies employed the primary efficacy outcome recommended by the FDA (haemostasis at a determined time point).

In the supportive studies, the primary efficacy outcomes varied from that recommended by the FDA. The efficacy outcomes in these studies therefore differed from those reported in the two pivotal studies, thus providing a parallel set of evidence that is difficult to compare.

The pivotal studies were assessed according to the quality criteria of the CONSORT statement (Schulz et al, 2010).<sup>19</sup> A summary is provided in Table 12.

**Table 12: Adequacy of the study**

Quality component	400-05-06	400-05-01
Power calculations performed	✓	✓
Inclusion and exclusion criteria provided	✓	✓
Method use to generate random allocation sequence	Computer generated randomisation schedules	Computer generated randomisation schedules
Mechanism used to implement the random allocation sequence	Sealed envelopes	Sealed envelopes
Treating physicians blinded to allocation	No (impractical)	No (impractical)
Outcome assessors blinded to allocation	Unclear	Unclear
Patients blinded to allocation	Unclear	Unclear
Comparator	Surgicel (active comparator)	Manual compression (active comparator)
Analysis according to ITT	✓	✓

ITT: intention to treat

Generally the studies were well conducted. Power calculations ensured that statistical differences could be demonstrated between the two treatment groups and the method of randomisation and its subsequent implementation appeared sound. Analysis was performed according to ITT. A major shortcoming of the studies was the fact that neither appeared to have blinded patients or outcome assessors to treatment allocation. The active comparators, Surgicel and manual compression, are widely used in Australia.

<sup>17</sup> EMEA, Committee for Medicinal Products for Human Use (CHMP), Month 2004. Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic Products, CPMP/BPWG/1089/00.

<sup>18</sup> FDA, Guidance for Industry; Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use, May 1999. Available at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm080795.pdf>

<sup>19</sup> Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine 2010, 8:18.

Both pivotal studies were randomised controlled trials (RCTs) which, when appropriately designed, conducted and reported, are the gold standard in evaluating health care interventions.<sup>19</sup> One study made no changes to the protocol after randomisation, while the other study made several non-substantial protocol clarifications prior to or at the commencement of randomisation. Neither study blinded the treating surgeon to treatment allocation, due to practical reasons. However, while it would have been possible and advantageous to blind outcome assessors and patients to treatment allocation, this was not reported to have taken place. Additionally, neither study clearly stated who the outcome assessors were. It was not clear whether the investigator was the surgeon performing the operation, or external personnel with unclear clinical credentials, and the clinical evaluator opinion advised that clinical outcomes should have been assessed by clinicians. Further, it was not reported that outcome assessors or patients were blinded.

In the opinion of the clinical evaluator, relapse and disease progression are likely to be unaffected by Evicel, as its role is to assist in immediate peri- and post surgical recovery. Evicel's recommended place among standard therapies is as an adjunct to existing methods for achieving haemostasis. This was supported by the fact that surgeons used other haemostatic methods prior to Evicel in the two pivotal studies.

The primary indication for Evicel is supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. A second indication is suture support for haemostasis in vascular surgery. These two indications have each been supported by RCT evidence, as both pivotal studies reported that haemostasis at either 4 or 10 minutes was significantly better with Evicel than with the comparative treatment. The supportive studies generally confirmed these findings.

The primary outcome, haemostasis at either 4 or 10 min is clinically relevant and no surrogate endpoints were required. The clinical evaluator confirmed that haemostasis and with it a reduction in blood loss, relates to a real clinical improvement. However the measurement of this outcome may be subjective, particularly as outcome assessors were not stated to be clinicians (who would be adept at assessing haemostasis). A recent Cochrane systematic review considered intra-operative blood loss (mL) to be an appropriate outcome. Both pivotal studies reported upon an additional issue of direct clinical and patient significance (length of hospital stay). In patients undergoing retroperitoneal or intra-abdominal surgery the mean length of hospital stay in Evicel patients was  $7 \pm 5$  nights, and in Surgicel patients was  $9.9 \pm 11.6$  nights. This suggests that length of hospital was shorter in Evicel patients but no conclusive statement may be made. Three patients from each treatment group did not have discharge dates and no statistical analysis was reported. In patients undergoing vascular surgery the mean length of stay in Evicel patients was  $5.1 \pm 8.1$  days and in Surgicel patients was  $5.5 \pm 6.2$  days. Again, no statistical analysis was reported. Overall the difference in length of stay between treatment groups was likely to be non-significant, given the wide ranges reported.

No efficacy concerns were identified regarding the use of Evicel in children <16 years, although the patient numbers in these subpopulations were small. The study of vascular surgery excluded paediatric patients from participating, hence the efficacy of Evicel in children undergoing vascular procedures is unknown but may well be equally effective. The sponsor stated that no development program is in place for the use of Evicel in paediatric patients and advised that the clotting mechanism of Evicel is identical for both adults and children, which was confirmed by the clinical evaluator.

The issues of optimal dose ranges and dosage regimens were not explored in the pivotal clinical studies. The dosages of Evicel used in these studies ranged from 0.5 to 10 mL. The safety and efficacy of larger dosages of Evicel have not been assessed in clinical trials. No dosage analysis was undertaken in any of the submitted studies.

Both pivotal studies excluded pregnant women from participating. The uncertainty regarding the safety and efficacy of Evicel in pregnant women has been highlighted in the proposed Australian PI. The PI notes the lack of evidence from human controlled clinical trials and states that animal studies are insufficient to assess Evicel's safety regarding reproduction, development of the embryo or foetus, the course of gestation and peri- and post natal development. The PI concludes that Evicel should be administered to pregnant and lactating women only if clearly required.

Both pivotal studies excluded patients requiring emergency surgery from their populations. It is unclear whether Evicel would prove effective in patients undergoing such surgery, who may have issues such as brisk bleeding or multiple bleeding sites.

One pivotal study followed patients for 5 weeks postoperatively, while the other study followed patients for 14 days post discharge. A longer length of follow up is unlikely to inform further upon the efficacy of Evicel, as it is promptly metabolised.

The sponsor stated that no formal interaction studies have been performed with the components of Evicel but that comparable products and thrombin solutions may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (such as antiseptic solutions). Application of Evicel to a patient's skin, where antiseptic solutions are likely to be present, may affect the efficacy of Evicel. It would be useful to mention this potential interaction in the PI. An analysis of Evicel patients who received heparin during vascular surgery did not indicate that heparin reduces the efficacy of Evicel.

There are some efficacy outcomes which remain to be informed by RCT evidence. It appears that differing quantities and/or thicker layers of Evicel may be applied, depending upon the application method. Neither pivotal study investigated the efficacy of Evicel which is applied by dripping compared with that applied by spraying. Additionally, the apparent variability in available spray nozzles introduces further uncertainty regarding this method of application.

The clinical trials involved application of Evicel to a single TBS; however, in surgical situations more than one TBS may exist. The studies did not explore the safety and efficacy of applying Evicel to more than one TBS per patient in one surgical procedure. It is possible that through repeated exposure to Evicel, patients could develop antibodies to the product which may reduce its efficacy in future surgeries.

## **Safety**

### **Introduction**

The sponsor presented two pivotal studies which assessed the safety of Evicel in patients undergoing retroperitoneal, intra-abdominal or vascular surgery. The sponsor stated that based on the comparability of Quixil and Evicel, clinical trials conducted using Quixil may be considered supportive of Evicel's safety. Eight clinical trials conducted using Quixil were presented as supportive previous human experience. Unlike Quixil, Evicel does not contain TA.

In the two pivotal studies, patients were followed up for between 14 days and 5 weeks post surgery. No patients were available beyond these periods. In the eight supportive studies, patients were generally monitored for adverse events up to 14 days post surgery and several studies monitored patients for serum virology until 6 months. No patients were followed beyond 6 months.

There were several limitations of the safety database in relation to the proposed target populations. The pivotal studies lacked long term safety follow up data relating to Evicel's use. Patients were exposed to Evicel on a single occasion, which does not inform on the

safety of multiple applications either during the same surgical procedure or over the course of several surgical procedures. As no immunological data were collected, it is unclear whether patients developed antibodies to Evicel.

The supportive studies did not assess the safety of Evicel but rather the safety of Evicel's precursor, Quixil. Patients were generally exposed to Quixil on a single occasion, which does not inform on the safety of multiple applications either during the same surgical procedure or over the course of several surgical procedures.

The TGA adopted EU guideline recommends that other safety aspects of fibrin sealant products include viral safety, transmissible spongiform encephalopathy (TSE) and immunogenicity.<sup>17</sup> Evicel is produced from human plasma and the sponsor noted that the risk of transmitting infectious agents has been minimised by strict screening procedures and two virus elimination steps during manufacture. The guideline recommends that appropriate clotting tests should be part of the study protocol and in case of pathological findings, specific testing for neutralising antibodies should be carried out. The evaluator was of the opinion that this level of monitoring was sufficient.

Both pivotal studies incorporated independent assessment of adverse events. In one study all safety monitoring was performed independently and in the other study independent clinical review of serious adverse events was performed.

Adverse events were recorded as they were reported, whether spontaneously volunteered by patients or in response to questioning. Monitoring of adverse events commenced from the baseline visit in one study and from the start of randomisation in the other. It was unclear how frequently patients were questioned and how spontaneous reporting took place (that is, whether patients report events to nursing staff, or only to study investigators). Adverse events were documented in the patient's medical record and case report form.

In the supportive studies safety monitoring was undertaken by an investigator, although it was unclear whether the investigator was the treating surgeon or another individual qualified to assess adverse events. It was not stated that the investigator was blinded to treatment group.

### **Patient exposure**

In the presented pivotal studies a total of 141 patients were treated with Evicel. Each patient was exposed to a single dose of Evicel which measured between 0.5 and 10 mL of combined product.

In the presented supportive studies a total of 226 patients were treated with Quixil (Table 13). Patients received at least one dose of Quixil which ranged from mean  $3.4 \pm 1.5$  mL to a maximum of 20 mL of combined product.



**Table 13: Supportive studies**

Study ID	N received Quixil	Adverse events follow up	Serology follow up	Quantity of Quixil administered
Vascular surgery				
Q-CVS-015-UK	10	Up to 30 days	-	Up to 10 mL
Liver surgery				
OFI-LIV-002-UK	21	Up to 14 days	-	Mean 12.0±5.0 (20). Two patients required a second application: one received an additional 3 mL (first application 5 mL), one received unknown additional amount (first application 20 mL)
Q-LIV-008 US	58	Up to 2 weeks	3 and 6 months	Up to 10 mL
OFI-LIV-003-B	17*	Up to 14 days	6 months	Mean 3.4±1.5 (16) mL
Orthopaedic surgery				
OFI-THR-005-UK	13	10 days	-	All patients had 10 mL administered apart from one patient who received 8 mL
Q-THR-009 US	54	Up to 2 weeks	3 and 6 months	Up to 10 mL
OFI-TKR-001-IL	29	At discharge	6 months	Mean 17.6±4.4 mL [10-20]
OFI-TKR-004-US	25	At discharge	6 months	10 mL

\*one patient did not receive Quixil

## Adverse events

### *Retroperitoneal or intra-abdominal surgery*

In patients undergoing retroperitoneal or intra-abdominal surgery, 46 of 67 Evicel patients (68.6%) suffered a total of 183 adverse events. In the Surgical treatment group 48 of 68 patients suffered a total of 200 adverse events (Table 14).

Table 14: Adverse events in patients undergoing retroperitoneal or intra-abdominal surgery

	Evicel (n=67)	Surgicel (n=68)
<b>Total number of adverse events</b>	183	200
<b>Number of patients with at least one event:</b>		
Adverse event	46 (68.7%)	48 (70.6%)
Serious adverse event	12 (17.9%)	15 (22.1%)
Severe adverse event	6 (9.0%)	10 (14.7%)
Adverse event requiring medical, surgical or other action	42 (62.7%)	46 (67.6%)
Related or possibly related adverse event	1 (1.5%)	2 (2.9%)

In these patients the most common adverse events were nausea (11.1%), hypokalaemia (11.1%), insomnia (10.4%), hypotension (10.4%) and pyrexia (9.6%). Events more commonly seen in Evicel patients included nausea (nine Evicel and six Surgicel patients) and insomnia (eight Evicel and six Surgicel patients), while hypotension was seen more commonly in Surgicel patients (nine Surgicel and five Evicel patients) (Table 15). There were no significant differences between the groups regarding the safety profile.

#### ***Vascular surgery***

One pivotal study and one supportive study assessed the safety of Evicel or Quixil during vascular surgery (400-05-01 and Q-CVS-015). No statistical analysis of differences between treatment groups was undertaken.

In the pivotal study, 48 of the 75 Evicel patients (64%) suffered a total of 113 adverse events and 51 of the 72 MC patients (70.8%) suffered a total of 158 adverse events (Table 16). In the supportive study nine of the 10 Quixil patients (90%) suffered a total of 21 adverse events and all of the control patients (100%) suffered a total of 28 adverse events. The most common adverse events were graft infection, nausea and pain.

**Table 15: Common adverse events in patients undergoing retroperitoneal or intra-abdominal surgery (Study 400-05-06)**

System Organ Class	Preferred Term	Evicel (n=67)	Surgicel (n=68)	Total (n=135)	Statistical Difference
Blood and Lymphatic System Disorders	Anaemia	3 (4.5%)	4 (5.9%)	7 (5.2%)	0.9839
Gastrointestinal Disorders	Nausea	9 (13.4%)	6 (8.8%)	15 (11.1%)	0.5632
	Vomiting	4 (6.0%)	1 (1.5%)	5 (3.7%)	0.3532
General Disorders and Administration Site Conditions	Oedema peripheral	6 (9.0%)	4 (5.9%)	10 (7.4%)	0.7241
	Pyrexia	7 (10.4%)	6 (8.8%)	13 (9.6%)	0.9776
Investigations	Haematocrit decreased	3 (4.5%)	4 (5.9%)	7 (5.2%)	0.9839
	Haemoglobin decreased	4 (6.0%)	4 (5.9%)	8 (5.9%)	0.7317
	Urine output decreased	3 (4.5%)	5 (7.4%)	8 (5.9%)	0.7317
Metabolism and Nutrition Disorders	Hyperglycaemia	2 (3.0%)	5 (7.4%)	7 (5.2%)	0.4495
	Hypokalaemia	8 (11.9%)	7 (10.3%)	15 (11.1%)	0.9757
	Hypomagnesaemia	3 (4.5%)	4 (5.9%)	7 (5.2%)	0.9839
Psychiatric Disorders	Anxiety	2 (3.0%)	4 (5.9%)	6 (4.4%)	0.6898
	Insomnia	8 (11.9%)	6 (8.8%)	14 (10.4%)	0.7554
Skin and Subcutaneous Tissue Disorders	Pruritus	5 (7.5%)	5 (7.4%)	10 (7.4%)	0.7609
Vascular Disorders	Hypertension	2 (3.0%)	5 (7.4%)	7 (5.2%)	0.4495
	Hypotension	5 (7.5%)	9 (13.2%)	14 (10.4%)	0.4136

**Table 16: Adverse events in patients undergoing vascular surgery**

Study ID	400-05-01		Q-CVS-015	
Treatment group	Evicel (n=75)	Control (n=72)	Quixil n=10	Control n=10
<b>Total number of adverse events</b>	113	158	21	28
<b>Number of patients with at least one event:</b>				
Adverse event	48 (64%)	51 (70.8%)	9 (90%)	10 (100%)
Serious adverse event	23 (30.7)	21 (29.2%)	0 (0%)	4 (40%)
Severe adverse event	13 (17.3%)	16 (22.2%)	0 (0%)	0 (0%)
Related/possibly related adverse event	9 (12%)	0 (0%)	0 (0%)	0 (0%)

In patients who received Evicel during vascular surgery (n=75) the most common adverse events were graft infection (6.1%) and nausea (5.4%) (Table 17). Events uniquely observed in MC patients were anaemia (n=5) and cardiac congestive failure (n=5). No statistical comparisons of adverse events between the Evicel and MC group were undertaken.

Additional observations related to safety were planned and performed during the study. Thirteen patients (17.6%) in the Evicel group and 13 patients (18.1%) in the MC group received postoperative blood transfusions. At postoperative wound assessment, seven patients (9.3%) in the Evicel group and nine patients (12.5%) in the MC group had a wound complication. At the 5-week follow up, 14 patients (19.2%) in the Evicel group and 13 patients (18.8%) in the MC group had a wound complication, which was mainly infection. Graft occlusion or thrombosis was reported in eight patients in each group.

**Table 17: Common adverse events in patients undergoing vascular surgery (study 400-05-01)**

System Organ Class	Preferred Term	Evicel (n=75)	MC (n=72)	Total (n=147)
Blood and Lymphatic System Disorders	Anaemia	0 (0%)	5 (6.9%)	5 (3.4%)
Cardiac Disorders	Cardiac Failure Congestive	0 (0%)	5 (6.9%)	5 (3.4%)
Gastrointestinal Disorders	Nausea	2 (2.7%) <sup>a</sup>	6 (8.3%)	8 (5.4%)
Gastrointestinal Disorders	Constipation	2 (2.7%)	5 (6.9%)	7 (4.8%)
General Disorders and Administration Site Conditions	Oedema Peripheral	5 (6.7%)	2 (2.8%)	7 (4.8%)
Infections and Infestations	Urinary Tract Infection	1 (1.3%)	4 (5.6%)	5 (3.4%)
Infections and Infestations	Graft Infection	4 (5.3%)	5 (6.9%)	9 (6.1%)
Injury, Poisoning and Procedural Complications	Vascular Graft Occlusion <sup>b</sup>	2 (2.7%)	5 (6.9%)	7 (4.8%)
Injury, Poisoning and Procedural Complications	Graft Thrombosis <sup>b</sup>	5 (6.7%)	0 (0%)	5 (3.4%)
Vascular Disorders	Hypotension	1 (1.3%)	5 (6.9%)	6 (4.1%)

a: reported in the study as 2.0%

b: In addition 4 patients (3 MC, 1 Evicel) had graft occlusion/ thrombosis coded by other MedDRA preferred terms: peripheral vascular disease (Evicel), AV Fistula thrombosis, Graft infection, Graft complication.

In patients who received Quixil during vascular surgery the most common adverse events included pain, pyrexia, hypotension, neck swelling and hypertension. No statistical comparison of adverse events between treatment groups was performed.

### ***Liver surgery***

Three supportive studies assessed the safety of Quixil during liver surgery. A summary of the adverse events is provided in Table 18. Of the 95 patients who were exposed to Quixil during liver surgery, 94 suffered one or more adverse events. The most commonly reported adverse events were fever, nausea, vomiting, pain, constipation, infection, coughing, tachycardia and hypertension.

**Table 18: Adverse events in patients who received Quixil during liver surgery**

Study ID	OFI-LIV-003-B (n=17*)	OFI-LIV-002-UK (n=21)	Q-LIV-008-US (n=58)
<b>Total number of adverse events</b>	153	186	NR
<b>Number of patients with at least one event:</b>			
Adverse event	16 (100%)	21 (100%)	57 (98.3%)
Serious adverse event	5 (29.4%)	5 (23.8%)	12 (20.7%)
Severe adverse event	3 (17.6%)	4 (19%)	11 (19%)
Related/possibly related adverse event	1	2	0

\* one patient did not receive Quixil  
NR: not reported

Two supportive liver surgery studies were comparative (OFI-LIV0003-B and Q-LIV-008-US). Of the 74 Quixil patients, 73 suffered at least one adverse event (98.6%). Of the 80 control patients, all suffered at least one adverse event (100%) (Table 19).

**Table 19: Comparative liver surgery safety**

Study ID	OFI-LIV-003-B		Q-LIV-008-US	
	Quixil (n=17*)	Control (n=17)	Quixil (n=58)	Control (n=63)
<b>Total number of adverse events</b>	153	133	NR	NR
<b>Number of patients with at least one event:</b>				
Adverse event	16 (100%)	17 (100%)	57 (98.3%)	63 (100%)
Serious adverse event			12	16
Severe adverse event	5	6	11	11
Related/possibly related adverse event	1	3	0	2

\* one patient did not receive Quixil

Two comparative studies were provided for patients who received Quixil during liver surgery (Q-LIV-008-US and OFI-LIV-003-B). The most common adverse events were fever, nausea, postoperative pain, pain, constipation, immune system disorders, diarrhoea, anaemia, hypertension, abdominal pain and vomiting.

In one study, dyspepsia (p=0.037) and gall bladder disorder (p=0.017) were reported with a higher frequency in control patients than in Quixil patients. The remaining comparative study did not conduct any statistical analysis of differences between treatment groups but noted a tendency towards a higher incidence of possible treatment related adverse events in the control group than the Quixil group (OFI-LIV-003-B).

### Orthopaedic surgery

Four supportive studies assessed the safety of Quixil during orthopaedic surgery. A summary of the adverse events is provided in Table 20. Of the 121 patients who received Quixil, 114 (94.2%) suffered at least one adverse event. The most commonly reported adverse events were pain, fever, nausea, anaemia, constipation and oedema peripheral.

**Table 20: Adverse events in patients who received Quixil during orthopaedic surgery**

Study ID	Q-THR-009 US (n=54*)	OFI-TKR- 001-IL (n=29)	OFI-TKR- 004-US (n=25)	OFI-THR- 005-UK (n=13)
<b>Total number of adverse events</b>	NR	NR	NR	12
<b>Number of patients with at least one event:</b>				
Adverse event	54 (100%)	27 (93%)	25 (100%)	8 (61.5%)
Serious adverse event	4	0	5	0
Severe adverse event	8	0	NR	NR
Related/possibly related adverse event	1	1	0	6

NR: not reported. \*includes 16 training patients and 38 controlled patients who received Quixil

Three supportive orthopaedic surgery studies were comparative (OFI-TKR-004-US, OFI-TKR-001-IL and Q-THR-009 US). Of the 92 Quixil patients, 89 suffered at least one adverse event (96.7%). Of the 101 control patients, 98 suffered at least one adverse event (97%) (Table 21).

**Table 21: Comparative orthopaedic surgery safety**

Study ID	OFI-TKR-004-US		OFI-TKR-001-IL		Q-THR-009-US*	
	Quixil (n=25)	Control (n=28)	Quixil (n=29)	Control (n=30)	Quixil (n=38)	Control (n=43)
<b>Total number of adverse events</b>	NR	NR	52	49	NR	NR
<b>Number of patients with at least one event:</b>						
Adverse event	25 (100%)	28 (100%)	26 (89.7%)	27 (90%)	38 (100%)	43 (100%)
Serious adverse event	5 (20%)	4 (14.3%)	0	1 (3.3%)	3 (7.9%)	5 (11.6%)
Severe adverse event	NR	NR	0	3 (10%)	3 (7.9%)	9 (20.9%)
Related/possibly related adverse event	0	0	1	0	0	0

\* does not include the 16 training patients as they were not enrolled in the controlled phase

Three comparative studies were provided for patients who received Quixil during orthopaedic surgery (OFI-TKR-004-US, OFI-TKR-001-IL and Q-THR-009-US). The most common adverse events were pain, fever, nausea, anaemia, constipation, urinary tract infection, oedema peripheral and urinary retention. Nausea was reported to be

significantly more common in control patients than in Quixil patients in one study ( $p=0.046$ ). Where reported, no other statistical differences were seen between treatment groups.

## **Serious adverse events and deaths**

### ***Deaths***

#### *Retroperitoneal or intra-abdominal surgery*

In patients undergoing retroperitoneal or intra-abdominal surgery, one patient who received Evicel died eight days postoperatively due to hepatorenal syndrome. This was deemed not relevant to study treatment. No deaths occurred in the Surgicel group during the 14 day follow up; however, one patient died 25 days postoperatively due to acute renal failure. This was deemed not relevant to study treatment.

#### *Vascular surgery*

In Study 400-05-01, four deaths occurred in the study population; two in the Evicel group and two in the MC group. The sponsor stated that none of the deaths were considered to have any relationship to the study treatment. In the Evicel group, the serious adverse events with subsequent death were severe bronchopneumonia (one month post surgery) in one patient and staphylococcal infection in the other. Despite the overall sponsor statement that no deaths were related to the study treatment, in the individual serious adverse event narratives provided it was stated that, in the opinion of the study investigator, the staphylococcal infection and the patient's subsequent death were possibly related to the study treatment. The exact cause and nature of this patient's death is unclear, as death occurred after hospital discharge. The death certificate gave the cause of death as renal failure. In the MC group, the serious adverse events with subsequent death were graft infection in one patient and acute abdomen, congestive cardiac failure, respiratory failure, and cardiac arrest in the other.

In Study Q-CVS-015-UK no deaths were reported.

#### *Liver surgery*

A total of four deaths occurred in patients who received Quixil during liver surgery. In Study Q-LIV-008-US one patient died due to multiple organ failure and bile duct tumour. This death was assessed as unlikely to be related to the study treatment. In Study OFI-LIV-002-UK there were three deaths. These were due to recurrence of liver cancer in one patient, massive cerebrovascular accident in one patient, and pneumonia, respiratory failure, hypotension and ventricular tachycardia in one patient.

Six deaths occurred in control patients and all occurred in one Study (Q-LIV-008-US). The causes of death were metastatic colon cancer with liver failure, liver failure, hepatic coma secondary to recurrent hepatoma, multiple organ failure, cholangiocarcinoma with obstructive jaundice and gastrointestinal haemorrhage.

#### *Orthopaedic surgery*

In the four orthopaedic studies no deaths were reported in patients who received Quixil. Two deaths were reported in control patients, where haemostasis was attempted through standard procedures alone. In one patient the cause of death was pneumonia and was considered unrelated to the study treatment. The second patient died due to a massive pulmonary embolism and no assessment was made regarding association to treatment group.



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***Serious adverse events (SAEs)******Retroperitoneal of intra-abdominal surgery***

In patients undergoing retroperitoneal or intra-abdominal surgery the most common SAEs were urinary retention (one each Evicel and Surgicel), abdominal abscess (one each Evicel and Surgicel) and ileus paralytic (one each Evicel and Surgicel). All other SAEs occurred only once.

One SAE (hepatorenal syndrome) was unresolved due to the patient's death. Two SAEs were reported to have been resolved with sequelae (one case of urinary retention and one case of postoperative ileus). No details were given regarding the patient with urinary retention, aside from medications taken after the onset of the SAE). The patient with postoperative ileus was discharged home with a Foley catheter, suprapubic tube irrigation regimen, skin staples and nephroureteral stents to bag drainage system. The outcome of one patient with deep vein thrombosis (DVT) was unclear as no further data was provided.

All remaining SAEs were resolved.

In Surgicel patients, one SAE (acute renal failure) was unresolved due to the patient's death. One SAE (urinary retention) was reported to have been resolved with sequelae. This patient was discharged to a rehabilitation facility with a urinary catheter in place and continued on treatment with sulfamethoxazole/trimethoprim. The outcome of one patient with small bowel fistula was unclear, as the patient was lost to follow up. All remaining SAEs were resolved.

***Vascular surgery***

Two studies reported safety outcomes for patients who received Evicel (pivotal study) or Quixil (supportive study) during vascular surgery.

In the pivotal study a total of 31 SAEs were reported in 23 patients in the Evicel group and 29 SAE were reported in 21 patients in the MC group. These numbers include the four events with an outcome of death.

In the supportive vascular surgery study (Q-CVS-015-UK) no SAEs occurred in the 10 patients who received Quixil. Four of 10 control patients had one SAE each: herpes zoster, lower respiratory tract infection, hypotension and pulmonary embolism.

***Liver surgery***

Among the 95 patients who received Quixil, 22 patients suffered at least one SAE each. The most frequent SAEs were infection, pain, hypotension, anaemia, pneumonia and sepsis, enlarged abdomen and pain.

In the two comparative studies, 17 of 75 Quixil patients and 22 of 80 control patients had one or more SAE.

***Orthopaedic surgery***

Among the 121 patients who received Quixil, a total of nine patients (including one training patient) suffered one or more SAE. Each event occurred in only one patient and events included paralytic ileus, ventricular tachycardia, urinary retention, haematoma, deep vein thrombosis, tachycardia, knee joint dislocation, cellulitis, oedema, chest pain, severe chills, fever, hypotension, acute kidney tubule necrosis, septic shock and kidney failure.

In the three comparative studies, eight of 92 Quixil patients and 10 of 101 control patients suffered one or more SAE.

## Adverse events with a possible causal relationship to Evicel

### *Retroperitoneal and intra-abdominal surgery*

In patients undergoing retroperitoneal or intra-abdominal surgery, three events in three patients were assessed by medical reviewers as having a possible relationship to the study treatment. These included one Evicel patient (1.5%) and two Surgicel patients (2.9%). The Evicel patient underwent an abdominal perineal resection to remove adenocarcinoma and suffered an abdominal abscess. One Surgicel patient underwent abdominal surgery for ileal pouch excision and end-ileostomy and suffered an abdominal abscess. One Surgicel patient underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and radical tumour debulking for uterine sarcoma and suffered a pelvic abscess. All of these events were reported to have been resolved.

### *Vascular surgery*

The number of adverse events and serious adverse events in the Evicel and MC vascular surgery groups was similar; however, there were differences in the number of adverse events possibly related to treatment. In the Evicel group, nine patients (12%) experienced 12 adverse events possibly related to treatment (Table 22). The sponsor stated that the events that occurred in the Evicel group are not unexpected in patients undergoing the surgical procedures carried out in the study. They also state that similar events were seen in the MC group but the investigators did not ascribe a causal relationship of any adverse event to MC as it was considered to be a standard surgical technique. This assigning of causal relationships only to the Evicel treatment could introduce bias. The study investigators were not blinded to treatment group, and may have been influenced by this knowledge. The actual reported incidences of adverse events do not appear to be different between the Evicel and MC groups.

**Table 22: Adverse events with a possible causal relationship with Evicel in 75 patients who received Evicel in vascular surgery**

System Organ Class	Preferred Term	N (%)
Infections and infestations	Graft infection	2 (2.67%)
	Staphylococcal infection	1 (1.3%)
Injury, poisoning and procedural complications	Vascular graft occlusion	1 (1.3%)
	Wound	1 (1.3%)
	Post procedural haematoma	1 (1.3%)
	Incision site haemorrhage (bleeding/ haematoma)	2 (2.67%)
	Postoperative wound complication	1 (1.3%)
Vascular Disorders	Haematoma	1 (1.3%)
General disorders and administration site conditions	Oedema peripheral	1 (1.3%)
Investigations	Decreased haemoglobin	1 (1.3%)

In patients who received Quixil during vascular surgery (Q-CVS-015-UK), the association of adverse events with treatment were usually reported as unrelated. Two events in the Quixil group (one event of hypoglossal nerve disorder and one of wound haemorrhage) and one in the control group (vagus nerve disorder) were considered unlikely to be related to treatment.

### ***Liver surgery***

In Quixil patients three adverse events were considered possibly related to treatment. These included one case of moderate, intermittent haemorrhage, one case of low haemoglobin and one case of blood loss; decreased haematocrit. Six adverse events were considered unlikely to be related to treatment group (one case of ascites, two cases of sepsis, two cases of Epstein-Barr virus (EBV) seroconversion; and one case of tonsillitis). Nine Quixil patients had 33 adverse events considered unlikely to be related to treatment.

In control patients, 13 adverse events were considered possibly related to treatment. These included one gall bladder disorder, one haematoma, one case of mild constant haemorrhage, five cases of moderate constant anaemia, one case of mild constant hypotension, one severe abscess under diaphragm, one case of moderate persistent intra-abdominal bleeding, one case of moderate bile leakage and one case of mildly elevated liver cytolytic enzymes. Two adverse events (EBV seroconversion, intubation for respiratory failure with bradycardia) were considered unlikely related to treatment group.

### ***Orthopaedic surgery***

One adverse event in the Quixil group was considered probably related to treatment (wound redness). Four Quixil patients had six adverse events which may have been related to Quixil treatment. Two of these patients suffered blisters at wound site, one patient suffered an infection at the drain site, and one patient suffered shortness of breath, muscle pain and chest pain. All events were reported to be resolved. Additionally, one Quixil training patient suffered mild peripheral oedema, which was considered possibly related to study treatment. Seventy five adverse events in the Quixil group were reported as unlikely to be related to treatment (63 Quixil and 12 training patients).

No adverse events in control patients were considered probably or possibly related to treatment. Forty four adverse events were reported as unlikely to be related to treatment.

### **Laboratory findings**

Several studies reported on the coagulation status of enrolled patients. This was measured using the activated partial thromboplastin time (aPTT), prothrombin time (PT) or international normalised ratio (INR).

Studies generally reported on abnormal laboratory findings, such as decreased haemoglobin, haematocrit or red blood cells (RBC) and anaemia. These findings may not be unusual in the postoperative setting, and may be due to actual blood loss or haemodilution due to fluid administration and third spacing of fluids.

### ***Retroperitoneal or intra-abdominal surgery***

In the pivotal Evicel study, patients undergoing retroperitoneal or intra-abdominal surgery had laboratory assessments (including coagulation parameters) performed within 24 hours prior to discharge. Evicel patients spent between 1-29 nights in hospital postoperatively (median 6 nights), while Surgicel patients spent between 1-63 nights (median 6 nights). No longer term data regarding return to normal levels were provided. The post surgery laboratory results were reviewed for possible clinical significance and clinically significant abnormal values were reported as adverse events.

In terms of coagulation, both treatment groups had an aPTT baseline of approximately 30 seconds. Both groups experienced an increase in aPTT after surgery: Evicel patients

increased by 2.0 [SD: 3.9] and Surgicel patients increased by 4.3 [SD: 20.8]. No statistical analysis was performed. Both treatment groups had a PT baseline of approximately 13 seconds. Both groups experienced an increase in PT after surgery: Evicel patients increased to 13.7 [SD: 2.5] and Surgicel patients increased to 14.0 [SD: 3.3]. Again, no statistical analysis was performed.

There were no significant differences between treatment group outcomes and none of the other clinically significant laboratory abnormalities were considered to be related to the study medication. Three adverse events were experienced by at least 5% of either treatment group (haematocrit decreased, haemoglobin decreased; urine output decreased). However, results were obtained for only 64/67 Evicel and 62/68 Surgicel patients and it is possible that the missing patients also had decreases in their haematocrit, haemoglobin or urine output. For all investigations, outcome parameters were similar for both treatment groups.

### ***Vascular surgery***

In the pivotal Evicel study, patients undergoing vascular surgery had a full blood count performed preoperatively, and on postoperative Day 1 or at time of discharge for day patients.

One Evicel patient (1.3%) and no MC patients had prolonged aPTT. Both treatment groups had a PT baseline of approximately 13 seconds and both groups experienced an increase in PT after surgery. In Evicel patients this increased to 13.7 [SD: 4.2] and in Surgicel patients increased to 13.5 [SD: 5.9]. No statistical analysis was performed. Both treatment groups had identical baseline INR results which persisted after surgery. Again, no statistical analysis was performed.

In the supportive study (Q-CVS-015-UK) there were no significant differences between the Quixil and alternative treatment group for postoperative decreases in haemoglobin ( $p=0.50$ ) or haematocrit ( $p=0.61$ ). Data for coagulation parameters were generally missing at baseline. This study performed a comparison of the absolute postoperative values and found no difference between treatment groups for either PT (Quixil mean 1.13 and Kaltostat mean 1.13) ( $p=0.88$ ) or aPTT (Quixil mean 1.13 and Kaltostat mean 1.12) ( $p=0.88$ ).

Postoperatively, haemoglobin had dropped by a mean of 15.8 g/L (SD 16.2) in the Evicel group and by a mean of 17.5 g/L (SD 15.7) in the MC group. Mean haematocrit did not drop postoperatively in the Evicel group and only dropped by 0.1 L/L (SD 0.1) in the MC group. Red blood cell count dropped by  $0.5 \times 10^9/L$  (SD 0.5) in the Evicel group and by  $0.6 \times 10^9/L$  (SD 0.5) in the MC group. White blood cell count rose by  $0.6 \times 10^{12}/L$  (SD 2.6) in the Evicel group and by  $1.7 \times 10^{12}/L$  (SD 3.2) in the MC group. Statistical comparisons between groups were not performed. The sponsor stated that no clinically relevant changes were noted from the preoperative to postoperative intervals in either group and there were no apparent differences between groups in the parameters assessed. The sponsor stated that none of the clinically significant laboratory abnormalities reported was considered to be related to the study treatment.

### ***Liver surgery***

In one supportive Quixil study (Q-LIV-008-US), the postoperative falls in haemoglobin and haematocrit were larger in the Quixil group but the difference between the two treatment groups was not statistically significant (at Day 1 postoperatively:  $p=0.60$  for haemoglobin;  $p=0.52$  for haematocrit). Postoperative changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were also not significantly different between treatment groups.

Regarding coagulation parameters, one Quixil patient and one control patient were each reported to have had a coagulation disorder, although no further details were provided. In

two Quixil patients and three control patients the time to coagulation increased and one Quixil patient and one control patient each had elevated PT.

Another supportive study (OFI-LIV-003-B) also found no significant differences between the Quixil and alternative treatment group for postoperative haemoglobin or haematocrit changes. The incidence of clinically significant abnormalities in AST, ALT, alkaline phosphatase, total bilirubin and urea was similar between the two treatment groups. Coagulation parameters were also similar between the groups and by discharge there was only one clinically significant value (one patient with elevated PT at baseline and at Day 14).

In a non-comparative study (OFI-LIV-002-UK), mean values for haemoglobin and haematocrit decreased postoperatively and had not returned to baseline by Day 14 or on discharge. In one patient the adverse event of low haemoglobin was identified as possibly treatment related, while in another a decrease in haematocrit was also possibly treatment related. Five Quixil patients had clinically significant changes at discharge in ALT, six Quixil had clinically significant changes at discharge in alkaline phosphatase and three Quixil patients had clinically significant changes in bilirubin. Three Quixil patients had reduced urea levels at discharge which were clinically significant. PT and aPTT values returned to normal by discharge.

### ***Orthopaedic surgery***

In a supportive comparative total hip replacement study (Q-THR-009-US), the postoperative change in haemoglobin was smaller in the Quixil group than the control group; however, this difference was not statistically significant ( $p=0.4253$ ). There was also no significant difference between groups for change in haematocrit. Four patients in the Quixil group and seven in the control group had increased coagulation time ( $p=0.528$ ).

Another total hip replacement study (OFI-THR-005-UK) found that there were no clinically significant values recorded for any individual patient for haemoglobin, haematocrit, PT or aPTT. Two patients who received Quixil had raised liver function test results, one of which was considered to be a mild adverse event but unlikely to be treatment related.

A comparative study in total knee replacement surgery (OFI-TKR-001-IL) stated that there were no discontinuations due to results of clinical laboratory tests. Postoperative changes in haemoglobin and haematocrit were not statistically different between treatment groups. For coagulation parameters, neither PT nor aPTT times after surgery differed significantly between the two treatment groups. One patient in the Quixil group had prolonged high prothrombin time listed as an adverse event.

Another comparative knee replacement study (OFI-TKR-004-US) found no statistically significant difference between treatment groups for haemoglobin and haematocrit changes from baseline to immediately post surgery; however, the decreases from baseline to Day 1 post surgery were significantly smaller in the Quixil group ( $p=0.002$  for haemoglobin;  $p<0.001$  for haematocrit). At discharge, one patient in the Quixil group and two in the control group had clinically significant abnormalities in glucose, one patient in the Quixil group and two in the control had clinically significant abnormalities in ALT and one patient in the Quixil group and two in the control had clinically significant abnormalities in AST. Urea levels were abnormal in one Quixil patient and the total bilirubin level was abnormal in one control patient. PT was prolonged in one Quixil patient at baseline and discharge.

### **Safety in special populations**

Presently, data are insufficient to support the safety of Evicel in children. Of 135 patients who underwent retroperitoneal and intra-abdominal surgery, only 11 patients were aged

16 years or younger and no patients were aged younger than 2 years (400-05-06). A total of four children received Evicel and seven received Surgicel and no adverse event was uniquely reported in Evicel patients. Both treatment groups experienced pyrexia (one Evicel patient [25%] and two Surgicel patients [28.6%]) and pruritus (one Evicel patient [25%] and one Surgicel patient [14.3%]). These events were also experienced by  $\geq 5\%$  of all patients in this study (n=135). The small number of paediatric patient prevents any further safety conclusions from being drawn.

More data are available regarding the safety of Evicel in adults aged  $\geq 65$  years. Of 135 patients who underwent retroperitoneal and intra-abdominal surgery, 52 patients were aged  $\geq 65$  years. A total of 30 adults aged  $\geq 65$  received Evicel and 22 adults aged  $\geq 65$  received Surgicel. Several adverse events were reported uniquely in Evicel patients. The most common events included: nausea (six patients [20%]), vomiting and constipation (three patients each [10%]), pancreatic leak, hypoglycaemia and pleural effusion (two patients each [6.7%]). The remaining unique Evicel adverse events were reported rarely (one event each, 3.3%). One adverse event which was assessed as possibly related to treatment occurred in an Evicel patient aged  $\geq 65$  (abdominal abscess). No statistical analysis of treatment group, patient age and adverse events was undertaken.

It was unclear whether the safety outcomes reported in the pivotal studies extend to patients who were excluded from participating. Excluded patients were those with known intolerance to blood products or to one of the components of the study product; those with autoimmune immunodeficiency diseases (including known HIV); those who were known, current alcohol and/or drug abusers; and female patients who were pregnant or nursing.

### **Immunological events**

The pivotal studies noted that commercially available Surgicel was provided for the clinical trial and was used within label and that the Evicel was used prior to expiry date.

No Evicel studies monitored antibody formation, thus all data regarding antibody formation is sourced from Quixil studies. The sponsor noted that the protein component and virus inactivation procedures for the Evicel are identical to those used for Quixil and hence that the viral safety of Evicel may be supported by the viral safety of Quixil. However, the below data are of only limited value as the compositions of Evicel and Quixil are different.

#### ***Vascular surgery***

In Study 400-05-01 a baseline serum sample was sent to the central laboratory for storage at  $-70^{\circ}\text{C}$  for 5 years following the end of the study in case any concerns arose regarding suspected blood borne viral transmission. However, no further reporting was provided. No serum testing was reported in Study Q-CVS-015-UK.

#### ***Liver surgery***

Each of the liver surgery studies conducted serum testing. In Study Q-LIV-008-US, 6 month follow up viral serology results were only available for 9 patients who were enrolled early in the study. None of these patients exhibited seroconversion.

In Study OFI-LIV-003-B, during 6 month follow up, changes in viral serology with respect to immunoglobulin G (IgG) antibodies were seen for seven patients in the Quixil group. The majority of changes were from positive to negative, although negative to positive seroconversions took place in two patients. In one patient serology for anti-hepatitis B (HB) changed to positive at 3 and 6 months, due to treatment for chronic active hepatitis B virus (HBV). In the other patient serology for anti-hepatitis A virus (HAV) changed to positive at 3 and 6 months due to a delayed response to vaccination. In this same patient

serology for Anti-cytomegalovirus (CMV) changed from negative to positive at 3 and 6 months due to an infection from the donor via the liver graft, which was confirmed by IgM antibodies. None of the seroconversions were judged to have been caused by the Quixil product.

In Study OFI-LIV-002-UK, all patients who tested positive to antibodies for viral markers at the 6 months follow up had either tested positive at baseline or the tests had not been performed at baseline. The study therefore states that there is no evidence to suggest that the study procedure caused seroconversion of the patients tested.

### ***Orthopaedic surgery***

Three orthopaedic supportive studies conducted serum testing. In Study Q-THR-009-US follow up serology results were available for 36 patients who were enrolled early in the study. None of these patients exhibited seroconversion. In Study OFI-TKR-001-IL, at the 6 month follow up there were no negative to positive seroconversions in the Quixil group. In Study OFI-TKR-004-US, at the 6 month follow up there were no negative to positive seroconversions in the Quixil group. One patient tested positive for anti-hepatitis A virus (HAV) IgG antibodies at 3 and 6 months but no baseline result was available.

### **Safety related to drug-drug interactions and other interactions**

The sponsor stated that no formal interaction studies have been performed with the components of Evicel but that comparable products and thrombin solutions may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (such as antiseptic solutions).

Concomitant heparin use was reported in one pivotal study. Due to its action as a blood thinning agent, it is feasible that heparin may interact with the clotting mechanism of Evicel or Quixil.

Only one patient undergoing retroperitoneal or intra-abdominal surgery received heparin and no investigation of interaction with Evicel was conducted (400-05-06). In Study 400-05-01 all patients received heparin before arterial clamping. The dose was approximately 70 IU/kg for femoral procedures or 35 IU/kg for upper extremity artery procedures; the exact dose administered was based on surgical judgement. The only analysis of complications between these two groups of patients was for potential bleeding related complications. MC patients exhibited more potential bleeding related complications than Evicel patients, regardless of the quantity of heparin administered. No statistical analysis of any relationship between heparin dosage and potential bleeding related complication was performed.

These complications included five patients per treatment group who suffered a haematoma and two patients per treatment group who suffered bleeding. Nine MC patients (12.5%) versus five Evicel patients (6.7%) suffered anaemia/low haemoglobin/low haematocrit. Events uniquely seen in MC patients were seroma and ecchymosis (one patient each), while two Evicel patients and no MC patients suffered increased sanguinous drainage.

### **Discontinuation due to adverse events**

Evicel is applied intra-operatively and is not considered an ongoing therapy. The sponsor states that there have been no marketing authorisation withdrawals, suspensions, or failure to obtain a marketing authorisation renewal for safety reasons.

None of the 141 patients who received Evicel in controlled studies were reported to have been withdrawn due to adverse events.

## Postmarketing experience

The sponsor provided two Periodic Safety Update Reports (PSURs) which collectively covered the period 6 October 2008 to 6 October 2009. Both PSURs stated that no regulatory action on the grounds of safety has been taken since the authorisation of Evicel in Europe (6 October 2008). Between 6 October 2008 and 6 April 2009 a total of 89,264 Evicel or Quixil kits were supplied internationally, while between 7 April 2009 and 6 October 2009 a total of 87,082 Evicel kits and 20,959 Quixil kits were supplied internationally. The sponsor noted that the number of kits supplied represents the number of patients exposed to either Evicel or Quixil, as most patients are treated with one kit. However, as adverse events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency (FDA 2010).

### *Evicel*

#### *PSURs*

The adverse events reported after Evicel use during October 2008 to October 2009 consisted of lack of efficacy (5 cases), deep vein thrombosis, severe soft tissue inflammatory reaction, slow healing, fluid accumulation and redness, and accidental exposure and included three severe adverse events.

An additional adverse event was reported in Late Breaking Information. A patient undergoing a hysteroscopy received Evicel via spray applicator to control cervical bleeding. One minute after application there was full cardiac arrest and death and the *post mortem* showed air within the vasculature including brain and heart. The pressure regulator was set at 37 pound-force per square inch (psi) to spray the Evicel and the proposed Australian labelling and packaging indicates that the pressure be no higher than 20-25 psi. It was suggested that this adverse event may have been due to the use of the spray applicator in an enclosed space. The reporting physician considered the event not related to Evicel but to the pressure regulator and the company physician considered the event not related to Evicel.

#### *Other sources*

An additional document was identified which addressed postmarketing experience with Evicel in the US market.<sup>20</sup> This document summarised the reported adverse events since product launch (September 2006) and up to March 2008. The data was not provided within the current clinical submission as it preceded the PSUR dates. Three serious adverse drug reactions, including two cases of fluid retention and one cerebrovascular accident were reported. The cerebrovascular accident was "...reported as hemiparesis during a carotid endarterectomy where Evicel was applied by spraying. Emergent angiography demonstrated patency of the carotid system and the intracranial circulation without evidence for thrombus or embolism. The surgeon felt that the most likely cause was hypoperfusion during clamping for the endarterectomy." The authors noted that the Evicel's applicator spray tip was held very close to the bleeding surface during spraying; about 5 cm instead of the recommended 10-15 cm. They concluded that a contribution of Evicel to this adverse event, either by a thrombogenic effect or by an incorrectly used spray device, could not be excluded. They recommended that the manufacturer provide appropriate instruction to surgeons on the correct use of the product.

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<sup>20</sup> European Medicines Agency, Assessment report for Evicel, 2008. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM192062.pdf>



The FDA also reported upon an adverse event where a patient suffered a fatal air embolism.<sup>21</sup> It is unclear whether this patient was the one discussed above.

Evicel was applied through a spray device attached to a wall unit at a higher than recommended pressure for the spray device. In addition, the spray head was placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant.

### **Quixil**

#### *PSURs*

The adverse events reported after Quixil use during October 2008 to October 2009 consisted of the following SAEs: fatal cardiorespiratory failure (2), air embolism (2), fatal intra-operative cardiac arrest, fatal multiple organ failure, fatal progressive liver insufficiency and status epilepticus. In three instances Quixil came into contact with the dura mater and patients suffered fatal cardiorespiratory or cardiac arrest. Two further patients who died after receiving Quixil were enrolled in an ongoing Netherlands prospective, randomised controlled study entitled "Efficacy of fibrin sealant in reducing resection surface – related complications after partial liver resections."

Other AEs consisted of fibrosis and lack of efficacy.

#### *Other sources*

Recent searches of the Manufacturer and User Facility Device Experience (MAUDE) database reveal that an additional Quixil adverse event took place after the PSUR 7 April 2009 to 6 October 2009 was produced.<sup>22</sup> During an autologous chondrocyte implantation (ACI) procedure the Quixil device was used to direct air into the knee cavity to dry it and to create a small defect to receive the ACI. During the drying procedure the patient deteriorated and died and a postmortem showed air embolism.

The surgeon planned to administer Quixil if there had been bleeding requiring control and was also planning to use Quixil to help hold the ACI in place. The company physician considered this fatal air embolism to be not related to the drug Quixil, which was not used in the procedure. Rather, it was considered that this was a case of device misuse and the Quixil device is not intended for administering air and hence was used off-label.

### **Evaluator's overall conclusions on clinical safety**

Due to the nature of the imprecise methods used to collect adverse event data in patients who received Evicel, the existence of additional events cannot be ruled out. This is particularly likely in the PSUR literature, where data is contributed voluntarily.

Dosages of up to 10 mL of Evicel were used in the pivotal trials, although no analysis of the relationship between adverse events and dosage of Evicel was provided. The sponsor stated that Evicel has no potential for overdose, abuse or re-bounce phenomena, and this was confirmed by the clinical evaluator.

No patients were reported to have withdrawn from the pivotal trials due to adverse events after receiving Evicel. Both studies stated that the observed adverse event profiles were as expected in these patient populations. Additionally, none of the clinically significant laboratory abnormalities (adverse events) reported was considered to be related to the

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<sup>21</sup> FDA. Risk of Life-Threatening Air or Gas Embolism with the Use of Spray Devices Employing Pressure Regulator to Administer Fibrin Sealants (Baxter Healthcare Corporation), 5 October 2009. Available from: <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm209778.htm>.

<sup>22</sup> FDA. MAUDE Adverse Event Report. Available from: [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi\\_id=1561922](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi_id=1561922)

study medication and there were no apparent differences between groups in the parameters assessed.

### ***Deaths attributed to adverse reactions***

Of 141 patients who received Evicel during clinical trials, a total of three patients died (2.1%). One patient who underwent retroperitoneal or intra-abdominal surgery died eight days postoperatively due to hepato-renal syndrome. This death was deemed not relevant to study treatment. Two patients who underwent vascular surgery also died. One patient suffered severe bronchopneumonia (one month post surgery) and the other patient suffered a staphylococcal infection. Despite the overall sponsor statement that no deaths were related to the study treatment, in the individual serious adverse event narratives provided it was stated that, in the opinion of the investigator, the staphylococcal infection and the patient's subsequent death were possibly related to the study treatment. The exact cause and nature of this patient's death is unclear, as death occurred after hospital discharge. The death certificate gave the cause of death as renal failure.

In the PSUR information one patient died after receiving Evicel via spray applicator during hysteroscopy. One minute after application the patient suffered full cardiac arrest and death and the post mortem showed air within the vasculature including brain and heart. The reporting physician considered the event not related to Evicel but to the pressure regulator and the company physician considered the event not related to Evicel.

Additional FDA literature reported that a further patient died after receiving Evicel during an unspecified surgical procedure.<sup>21</sup> The patient suffered a fatal air embolism after Evicel was applied through a spray device attached to a wall unit at a higher than recommended pressure for the spray device. In addition, the spray head was placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant.

It may be prudent for the sponsor to provide clinician education and training in the correct and safe use of spray applicators. Alternatively, the sponsor may mandate that spray application of Evicel should not be undertaken until further studies establishing the safety of this application method are conducted.

### ***Serious adverse reactions***

Of the 141 patients who received Evicel during controlled trials, 35 patients (24.8%) experienced a total of 47 SAEs. In patients who underwent retroperitoneal or intra-abdominal surgery the SAEs included atrial fibrillation, small intestinal obstruction, ileus paralytic, jaundice, hepatorenal syndrome (patient died), abdominal abscess (related to treatment), right lobe pneumonia, staphylococcal infection, hypoglycaemia, compartment syndrome, urinary retention, hypoxia, atelectasis, thrombophlebitis, symptomatic orthostatic hypotension and DVT. Each event occurred only once. One of these events was reported to be possibly related to treatment (abdominal abscess). One SAE (hepatorenal syndrome) was unresolved due to the patient's death. Two SAEs were reported to have been resolved with sequelae (one case of urinary retention and one case of postoperative ileus). The outcome of two patients was unclear (one case of DVT and one case of urinary retention). All remaining SAEs were resolved.

In patients who underwent vascular surgery, those SAEs which were reported to have been resolved included: localised infection, wound infection, vascular graft occlusion, urinary tract infection (UTI), haematoma, arteriovenous graft thrombosis, chronic renal failure, myocardial infarction, hemiparesis, incision site haemorrhage (two patients), ventricular tachycardia/atrial tachycardia/supraventricular extrasystoles, graft thrombosis (four patients), post procedural haematoma, peripheral vascular disorder and oedema peripheral.

The incidence of graft thrombosis in patients who received Evicel may be an issue of concern. Although no significant difference was seen between treatment groups regarding this event, it was not clearly defined whether this event occurred due to the nature of the surgery or due to Evicel.

SAEs which resulted in patient death included one case each of bronchopneumonia and staphylococcal infection. SAEs which were reported to have been resolved with sequelae included one case each of graft infection, peripheral ischaemia, haemorrhoids/anaemia/rectal haemorrhage, hypoaesthesia and upper GI haemorrhage. Two SAEs were reported to be ongoing (incision site cellulitis and respiratory failure) and no details were provided on the two remaining SAEs (abdominal sepsis and intestinal fistula).

The PSUR information revealed that three additional SAEs were experienced in patients who received Evicel. One patient who received Evicel during excision of an epigastric abdominal wall lipoma experienced a severe soft tissue inflammatory reaction and lipoma recurrence. The reporter considered the event to be possibly related to Evicel. Two patients who received Evicel during total knee replacement each suffered a deep vein thrombosis. Causation has not been provided as both cases are still open.

A further document which addressed post marketing experience with Evicel in the US market between September 2006 and March 2008 revealed that three additional serious adverse drug reactions were reported.<sup>20</sup> Two cases of fluid retention occurred; however, no further details were provided on and causality was not established. One patient suffered a cerebrovascular accident during a carotid endarterectomy after Evicel was applied by spraying. Although the surgeon felt that the most likely cause was hypoperfusion during clamping for the endarterectomy, Evicel's applicator spray tip was held very close to the bleeding surface during spraying; about 5 cm instead of the recommended 10-15 cm. The document concluded that a contribution of Evicel to this adverse event, either by a thrombogenic effect or by an incorrectly used spray device, could not be excluded.

#### *Serious adverse events with a possible relationship to Evicel*

Of 141 patients who received Evicel during controlled trials, ten patients (7.1%) experienced 13 adverse events which were assessed by medical reviewers as having a possible relationship to the study treatment. One patient underwent an abdominal perineal resection to remove adenocarcinoma, and suffered an abdominal abscess. The event was reported to have been resolved. The remaining events occurred in patients undergoing vascular surgery and included graft infection in two patients, occluded graft in one patient, superficial small right groin wound in one patient, staphylococcus infection in one patient, left arm haematoma, left arm oedema and decreased haemoglobin all in the same patient, right groin haematoma in one patient, abdominal incision bleeding and haematoma in one patient, and bilateral groin open post procedural wound in one patient. The sponsors state that these events are not unexpected in patients undergoing the surgical procedures carried out in the study.

### **List of questions**

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

### **Efficacy**

*A brief analysis of patients who received varying doses of heparin during vascular surgery suggests that heparin doses of between 35-70 IU/kg did not appear to compromise haemostasis at 4 minutes. Further drug interaction studies are required in order to ascertain*

*any relationship between Evicel and heparin (and any other drugs). Additionally, the effect of antiseptic solution on Evicel's efficacy is presently unknown. Does the sponsor plan to undertake such studies?*

The sponsor replied that it did not intend to evaluate the heparin dose response relative to the haemostatic effectiveness of Evicel. As an adjunctive haemostasis product that is used locally on a specific bleeding site or area, ascertaining systemic drug interaction will also not be plausible.

The sponsor also did not intend to evaluate the effects of antiseptic solutions on Evicel. During surgery, antiseptic solutions are superficially applied for surgical preparations compared to where Evicel is to be used as an adjunct to haemostasis during surgery therefore ascertaining a relationship will not be warranted.

*Additional research indicates that the sponsor provided an additional randomised, comparative study of 121 patients undergoing liver surgery to the FDA in order to obtain FDA clearance for Evicel.<sup>9</sup> Would the sponsor be able to provide a reason for excluding this study from this submission?*

The sponsor indicated that the exclusion of this clinical study report was an oversight, and a copy of the study report was provided.

*Both pivotal studies excluded pregnant women and patients undergoing emergency surgery from their populations. Does the sponsor plan to undertake additional research to investigate the safety and efficacy of Evicel in these patients?*

The sponsor noted that elective surgery is generally avoided on pregnant women due to the potential risks. There are ethical, legal, financial and scientific concerns that would make the conduct of a randomized controlled trial evaluating the efficacy of a fibrin sealant in pregnant women impossible to develop. The overseas sponsor does not intend to evaluate additional research to investigate Evicel in these populations.

Patients undergoing emergency surgery were excluded from the pivotal studies primarily due to the informed consent process requirement in conducting clinical studies. The study was conducted on subjects undergoing elective procedures that can provide their informed consent to participate in the study. This would be challenging in emergent cases, as the sponsor believed that the difference between the elective or emergency nature of the surgery should have no impact on haemostasis on the target bleeding sites evaluated in the population included in the clinical trials.

*Neither pivotal study investigated the efficacy of Evicel which is applied by dripping compared with that applied by spraying. Additionally, the apparent variability in available spray nozzles introduces further uncertainty regarding this method of application. Does the sponsor plan to conduct any research to inform further on this issue?*

The sponsor has conducted *in vitro* tests evaluating the difference between the two application techniques (dripping versus spraying) to determine if the difference impacts on the product's efficacy as a dural sealant. Although the tests showed that the spray technique may form a more cohesive seal, this may not translate to any clinical significance when used as an adjunct to haemostasis. Although with some variability, the tests show that in both application techniques, 100% of the efficacy is above the typically applied pressure during a valsalva manoeuvre.

When used as an adjunct to achieve haemostasis during surgery, the variability of the anatomy of the bleeding sites must be considered. Dripping would allow surgeons more accuracy in targeting a smaller more specific bleeding site while spraying would allow surgeons to cover a broader surface area.

## Safety

*At least two patients are known to have died after receiving Evicel via spray applicator. Would the sponsor provide and/or promote clinician education and training in the correct and safe use of spray applicators? If not, would the sponsor be willing to recommend that spray application of Evicel should not be undertaken until further studies establishing the safety of this application method are conducted?*

The sponsor indicated that the safety of Evicel has been established in 3 pivotal randomised controlled trials. The concern of potential air embolism during spray application was identified during routine pharmacovigilance activities. During the investigation and interactions with other Health Authorities this issue was concluded to be associated with the misuse of the product at higher than recommended pressures and/or in close proximity to the tissue surface. In the USA and Canada this warning was directed at all Fibrin Sealants utilising a spray application. In the EU similar warnings were provided for other marketed fibrin sealants. When used according to the instruction, the sponsor believes that the spraying application is a safe method.

When the risk of air embolism associated with spray application was communicated, the following items were actioned to ensure increased safety. The IFU has been revised to provide more details regarding these risks and a clarifying letter to health care providers alerting the possibility of air or gas embolism and the proper use of the product has been communicated. The Risk Management Plan (RMP) also provides information that the sponsor holds professional education programs on the use of adjunctive haemostats and sealants periodically throughout the year at various training facilities. As part of the educational program the surgeons will be instructed on the correct use of the product including dose and application.

In Australia the launch campaign will have a strong emphasis on professional education and correct use of the product prior to use in patients. For instance there are plans for extensive training for surgeons in animal labs prior to use in patients. There are provisions to organise a product specialist to be present during surgeries initially to ensure safe use when the product is launched and training will be provided to the nursing staff on the handling, receipt and storage of the product.

*Due to the limited, long term patient exposure to Evicel, a theoretical risk for immunogenicity and for allergic reaction remains. Additionally there is an increased risk of transfer of infectious material as Evicel is manufactured from human blood products. Does the sponsor plan to conduct further research with long-term follow up and repeated patient exposure?*

Evicel is derived from human pooled plasma and will be absorbed by the patient's natural process within 7-14 days. The sponsor would need further clarification on the concern regarding long term effects.

Although there is a theoretical risk of immunogenicity and allergic reactions on repeated exposure to plasma derived fibrin sealants, the sponsor does not plan to conduct further clinical research with long term follow up and repeated patient exposure.

Since Evicel is derived from human plasma the theoretical risk of immunogenicity and/or allergic reaction is expected to be significantly less than that of bovine derived products that are currently available on the market and are regularly used during surgery. The donor selection steps, viral removal/filtration and inactivation steps and other precautionary steps taken during the manufacture process were all incorporated to maximise the product's safety. The risk of transfer of infectious materials remains a theoretical risk.

The design of such a clinical trial evaluating these risks will make it highly improbable to execute because of the sample size that will be required for detection if a signal exists

within a given population. The sponsor believed that this is potentially best handled during the postmarket pharmacovigilance surveillance. As of the last periodic safety update, where approximately 165,000 units of Evicel were sold worldwide, there has been no incidence of immunogenicity or allergic reaction reported to the sponsor.

*Dose response studies were not conducted. Does the sponsor plan to conduct such studies?*

The sponsor requested further clarification on what attribute regarding dose response is of concern so that an appropriate response can be provided. In general, the sponsor believed that clinical studies conducted support the products clinical safety as seen by the adverse event profile in three pivotal randomised, controlled, clinical studies and supported by the current pharmacovigilance monitoring.

*The issue of graft thrombosis in patients undergoing vascular surgery remains a concern. Although no significant difference was seen between treatment groups regarding this event, it was not clearly defined whether this event occurred due to the nature of the surgery or due to Evicel. Can the sponsor provide any additional data indicating the causality of this adverse event?*

This study involved vascular reconstructions utilising ePTFE grafts with at least one graft-to-femoral artery anastomosis or an upper extremity ePTFE AV access graft. As expected, both groups (Evicel and MC) contained high risk subjects in whom these types of synthetic vascular grafts have well described risks for thrombotic/occlusive adverse events (early and late). The total number of thrombotic/occlusion adverse event (TOAEs) was the same between the groups during the study period (8 in each group). Thus, the overall primary graft patency rate through the study follow up period was essentially identical between groups and was within the range expected in this population with these ePTFE graft procedures (Evicel = 89.3%; MC = 88.9%). Each group had 5 AV grafts and 3 bypass grafts fail. All of these 16 events were reviewed in detail.

When all 16 graft failure events are considered, there were a similar number of early failures (within 7 days of the index surgical event) across treatment groups; there were 5 TOAEs (4 if the non-thrombotic event is excluded) in the Evicel group and 3 in the MC group. Careful review of the early failures in each group suggests that clinical/anatomical circumstances (long extra anatomic ePTFE bypass, ePTFE femoral-tibial bypass, early postoperative hypotension etc) were likely to have been causative rather than the treatment of mild to moderate anastomotic bleeding during surgery with either manual compression or with the Evicel. Between Days 7 to 12, there was one additional Evicel patient who was reported to have had an arteriovenous (AV) graft thrombosis. This was not reported as an SAE and no more detail surrounding the event was provided.

Since the overall primary graft patency rate was the same across groups and was within the expected range and the number of early graft failures was similar across groups (Evicel = 5; MC = 3) and since clinical circumstances appear to have been likely to have been causative for graft failure, it is not felt that this study suggests an elevated risk for graft thrombosis or occlusion when Evicel is used to treat mild to moderate anastomotic bleeding in vascular reconstructions involving an ePTFE graft.

These questions have been raised previously by the EU prior to approval. In addition to the information provided above, the sponsor is conducting a Post Approval Safety Surveillance (PASS) study using Evicel as an adjunct to haemostasis during peripheral vascular surgery. That study was initiated in June 2010 and is currently ongoing with approximately 80 out of 300 subjects enrolled. To date, there has been no safety signals detected that confirms Evicel to be a contributing factor in graft occlusions or thrombosis when used during vascular surgery. The protocol for that study has been provided to TGA as requested during the RMP review.

*Does the sponsor plan to conduct any further safety and efficacy studies in patients with other surgical indications (that is, other than gynaecologic, urologic, general or vascular surgery)?*

The sponsor indicated that a clinical study evaluating the safety and efficacy of Evicel when used as an adjunct to sutured dural repair in elective cranial surgery to provide intra-operative watertight closure has been initiated in the EU.

## **Product Information/ Consumer Medicine Information**

The clinical evaluator also posed questions relating to the PI and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

## **Clinical summary and conclusions**

### **Clinical aspects**

#### ***Clinical efficacy***

##### *Dose response studies and main clinical studies*

No dose response studies were conducted. Two main pivotal studies were presented which assessed patients undergoing gynaecologic, urologic, general or vascular surgery. The efficacy of Evicel in patients with other types of surgical indications is unknown.

Additional research indicates that the sponsor provided an additional randomised, comparative study of 121 patients undergoing liver surgery to the FDA in order to obtain FDA clearance for Evicel.<sup>9</sup> The primary efficacy endpoint was haemostasis at either 4 or 10 minutes. In patients undergoing retroperitoneal or intra-abdominal surgery (Study 400-05-06), more patients in the Evicel group (63/66, 95.5%) achieved haemostasis at 10 min compared with the Surgicel group (56/69, 81.2%) (RR 1.18 [95% CI 1.04, 1.36]) (P<0.05). The relative proportions of haemostatic success at 4 and 7 min were consistent with the haemostatic outcome at 10 min (P<0.05). Subgroup analyses for the adult, adult 65+ and paediatric age groups were performed and each found that more Evicel than Surgicel patients achieved haemostasis at 4, 7 and 10 min. No statistical differences were reported.

The incidence of treatment failure (failure to achieve haemostasis at 10 min or the need to administer additional haemostatic measures during the 10 min observation period) was higher in the Surgicel group than the Evicel group. No statistical differences were reported. Significantly more Surgicel patients (4/69) required additional haemostatic measures during the 10 min observation period than Evicel patients (0/66) (p=0.05). Failures due to brisk bleeding occurred exclusively in Surgicel subjects (2 adult and 2 paediatric patients) (p=0.05 versus Evicel patients).

In patients undergoing vascular surgery (Study 400-05-01) more patients in the Evicel group achieved haemostasis at 4 min compared with the MC group (P<0.001). This finding was confirmed by all analysis types (FAS original model, FAS revised model, FAS worst case model, PP original model, PP revised model).

The overall incidence of treatment failure (the presence of bleeding at the SAS at 10 min or the need to administer additional haemostatic measures during the 10 min observation period) was higher in the MC group than the Evicel group (OR for original model 0.14; 95% CI 0.05 – 0.45; P<0.001; OR for revised model 0.18; 95% CI 0.07 – 0.48; P<0.001). This was mainly due to the persistence of bleeding at the end of the 10 min observation period in more patients in the MC group. However it should be noted that in both groups there is a discrepancy between the percentage of patients recorded as having treatment success (haemostasis at 10 min) and the percentage recorded as a treatment failure. The

three Evicel subjects who required other haemostatic measures were included by the sponsor as treatment successes, which could be misleading.

The secondary efficacy endpoint was TTH. In patients undergoing retroperitoneal or intra-abdominal surgery (Study 400-05-06) TTH was significantly lower in the Evicel group (range 0.3 to 8.1 min, median 2.3) than in the Surgicel group (0.8 to 9.8 min, median 3.4) ( $p < 0.001$ ). Subgroup analyses for the adult, adult 65+ and paediatric age groups were performed and each found that TTH was lower in Evicel than in Surgicel patients. No statistical differences were reported. Additional analyses revealed that TTH success rates were better in the mild bleeding group (100% for Evicel and 89.2% for Surgicel) compared to the moderate bleeding group (88.5% for Evicel and 71.9% for Surgicel).

In patients undergoing vascular surgery (Study 400-05-01), more patients in the Evicel group achieved haemostasis at 7 and 10 min compared with the MC group. Using the FAS, at 7 min 68/75 participants (90.7%) in the Evicel group and 43/72 (59.7%) in the MC group had achieved homeostasis (OR for original model 7.9; 95% CI 2.8 – 21.9;  $p < 0.001$ ; OR for revised model 6.5; 95% CI 2.6 – 16.1;  $p < 0.001$ ). Again using the FAS, haemostasis at 10 min was achieved in 72/75 participants (96.0%) in the Evicel group and 50/72 (69.4%) in the MC group (OR for original model 18.5; 95% CI 3.7 – 91.8;  $p < 0.001$ ; OR for revised model 10.9; 95% CI 3.1 – 38.8;  $p < 0.001$ ).

The findings of a benefit of Evicel are clinically as well as statistically relevant because it is widely accepted in the surgical community that reducing bleeding time in surgery, and with it reduced blood loss, is better for patients.

Both pivotal studies reported upon an additional issue of clinical significance (length of hospital stay). In patients undergoing retroperitoneal or intra-abdominal surgery the mean length of hospital stay in Evicel patients was  $7 \pm 5$  nights and in Surgicel patients it was  $9.9 \pm 11.6$  nights. This suggests that length of hospital was shorter in Evicel patients but no conclusive statement may be made. Three patients from each treatment group did not have discharge dates and no statistical analysis was reported. In patients undergoing vascular surgery the mean length of stay in Evicel patients was  $5.1 \pm 8.1$  days and in Surgicel patients it was  $5.5 \pm 6.2$  days. Again, no statistical analysis was reported. Overall the difference in length of stay between treatment groups was likely to be non-significant, given the wide ranges reported.

#### *Clinical studies in special populations*

Special studies in children, the elderly and patients with renal or hepatic impairment were not conducted. One pivotal study (400-05-06) performed subgroup analyses in children  $< 16$  years and in adults aged 65+. Regardless of age, haemostatic success with Evicel measured between 90% and 100% yet with Surgicel measured between 71% and 86%. The low numbers in the paediatric group make definitive conclusions difficult.

Adults aged 65+ had a longer TTH than the ITT analysis (the whole study population) and their haemostatic success at 10 min was lower. Paediatric patients achieved haemostasis more quickly and with more success than the ITT analysis. However, no statistical analyses on these sub-populations were performed and the limited number of patients studied restricts the applicability of the outcomes measured.

#### *Supportive studies*

The findings of the supportive studies generally confirmed the findings of the pivotal studies. Two studies measured TTH and found that this was significantly lower in patients who received Quixil than in patients who received control treatments ( $p = 0.0015$  in one study of 20 vascular surgery patients;  $p = 0.011$  in 121 liver surgery patients).

Four supportive studies reported on blood loss (mL), hence these results are not directly comparable to the pivotal Evicel studies. One study found no significant difference in intra-



operative blood loss between treatment groups in 34 liver surgery patients ( $p=0.73$ ). One study found that postoperative blood loss was significantly lower in Quixil patients than in control patients ( $p<0.001$  in 53 orthopaedic surgery patients). Two studies found that total blood loss was significantly lower in Quixil patients than in control patients ( $p=0.0071$  in 81 orthopaedic surgery patients; and  $P<0.001$  in 59 orthopaedic surgery patients).

### ***Clinical safety***

#### *Patient exposure*

No dose response studies were conducted. Two main pivotal studies were presented which assessed patients undergoing gynaecologic, urologic, general or vascular surgery. The safety of Evicel in patients with other types of surgical indications is unknown. A total of 141 patients were exposed to a single dose of Evicel which measured between 0.5 and 10 mL of combined product.

#### *Adverse events*

Due to the nature of the imprecise methods used to collect adverse event data in patients who received Evicel, the existence of additional events cannot be ruled out. This is particularly likely in the PSUR literature where data is contributed voluntarily.

No patients were reported to have withdrawn from the pivotal trials due to adverse events after receiving Evicel. Both studies stated that the observed adverse event profiles were as expected in these patient populations. Additionally, none of the clinically significant laboratory abnormalities (adverse events) reported was considered to be related to the study medication and there were no apparent differences between groups in the parameters assessed.

#### *Serious adverse events and deaths*

Of 141 patients who received Evicel during clinical trials, a total of three patients died (2.1%). Despite the overall sponsor statement that no deaths were related to the study treatment, in the individual serious adverse event narratives provided it was stated that, in the opinion of the investigator, the staphylococcal infection and the patient's subsequent death were possibly related to the study treatment.

In the PSUR information one patient died after receiving Evicel via spray applicator during hysteroscopy. The reporting physician considered the event not related to Evicel but the pressure regulator and the company physician considered the event not related to Evicel.

Additional FDA literature reported that a further patient died after receiving Evicel during an unspecified surgical procedure.<sup>21</sup> The Evicel was applied through a spray device attached to a wall unit at a higher than recommended pressure for the spray device and the spray head was placed at a distance from the bleeding site that was closer than the recommended distance guidelines for the application of the sealant.

It may be prudent for the sponsor to provide clinician education and training in the correct and safe use of spray applicators. Alternatively, the sponsor may mandate that spray application of Evicel should not be undertaken until further studies establishing the safety of this application method are conducted.

Of the 141 patients who received Evicel during controlled trials, 35 patients (24.8%) experienced a total of 47 SAEs. Ten of these events were reported to be possibly related to treatment, one of which occurred in a patient who underwent an abdominal perineal resection (abdominal abscess). The remaining SAEs which were deemed possibly related to Evicel occurred in patients undergoing vascular surgery and included graft infection in two patients, occluded graft in one patient, superficial small right groin wound in one patient, staphylococcus infection in one patient, left arm haematoma, left arm oedema and decreased haemoglobin all in the same patient, right groin haematoma in one patient, abdominal incision bleeding and haematoma in one patient and bilateral groin open post

procedural wound in one patient. The incidence of graft thrombosis in vascular surgery patients who received Evicel may be an issue of concern. Although no statistically significant difference was seen between treatment groups regarding this event, it was not clearly defined whether this event occurred due to the nature of the surgery or due to Evicel.

SAEs which resulted in patient death included one case each of bronchopneumonia and staphylococcal infection.

The PSUR information revealed that three additional SAEs were experienced in patients who received Evicel. One patient who received Evicel during excision of an epigastric abdominal wall lipoma experienced a severe soft tissue inflammatory reaction and lipoma recurrence. The reported considered the event to be possibly related to Evicel. Two patients who received Evicel during total knee replacement each suffered a deep vein thrombosis. Causation has not been provided as both cases are still open.

A further document which addressed postmarketing experience with Evicel in the USA market between September 2006 and March 2008 revealed that three additional serious adverse drug reactions were reported.<sup>20</sup> Two cases of fluid retention occurred; however, no further details were provided on and causality was not established. One patient suffered a cerebrovascular accident during a carotid endarterectomy after Evicel was applied by spraying. The document concluded that a contribution of Evicel to this adverse event, either by a thrombogenic effect or by an incorrectly used spray device, could not be excluded.

#### *Laboratory findings*

Studies generally reported on abnormal laboratory findings such as decreased haemoglobin, haematocrit or red blood cells (RBC) and anaemia. These findings may not be unusual in the postoperative setting and may be due to actual blood loss or haemodilution due to fluid administration and third spacing of fluids.

Both pivotal studies stated that there were no significant differences between treatment group outcomes and none of the clinically significant laboratory abnormalities reported was considered to be related to the study medication.

#### *Safety in special populations*

Presently, data are insufficient to support the safety of Evicel in children. Of 135 patients who underwent retroperitoneal and intra-abdominal surgery, only 11 patients were aged 16 years of younger and no patients were younger than 2 years old. A total of four children received Evicel and seven received Surgicel and no adverse event was uniquely reported in Evicel patients. The small number of paediatric patients prevents any definitive safety conclusions from being drawn. No statistical analysis of treatment group, patient age and adverse events was undertaken.

It is unclear whether the safety outcomes reported in the pivotal studies extend to patients who were excluded from participating. Excluded patients were those with known intolerance to blood products or to one of the components of the study product; those with autoimmune immunodeficiency diseases (including known HIV); patients requiring emergency surgery; those who were known, current alcohol and/or drug abusers; and female patients who were pregnant or nursing.

#### *Immunological events*

No Evicel studies monitored antibody formation, thus all data regarding antibody formation is sourced from Quixil studies. The sponsor notes that the protein components and virus inactivation procedures for the Evicel are identical to those used for Quixil and hence that the viral safety of Evicel may be supported by the viral safety of Quixil.

However, the Quixil immunological data are of only limited value as the compositions of Evicel and Quixil are different.

In patients undergoing liver surgery, changes in viral serology with respect to IgG antibodies were seen for seven patients in the Quixil group. The majority of changes were from positive to negative, although negative to positive seroconversions took place in two patients. None of the seroconversions were judged to have been caused by the Quixil product. In patients undergoing orthopaedic surgery, one patient tested positive for anti-HAV IgG antibodies at 3 and 6 months but no baseline result was available.

#### *Safety related to drug-drug interactions and other interactions*

Concomitant heparin use was reported in one pivotal study where all patients received heparin before arterial clamping. The dose was approximately 70 IU/kg for femoral procedures or 35 IU/kg for upper extremity artery procedures; the exact dose administered was based on surgical judgement. MC patients exhibited more potential bleeding related complications than Evicel patients, regardless of the quantity of heparin administered. No statistical analysis of any relationship between heparin dosage and potential bleeding related complication was performed.

No assessment of interactions between Evicel and any other medications was reported.

#### *Discontinuation due to adverse events*

Evicel is applied intra-operatively and is not considered an ongoing therapy. The sponsor stated that there have been no marketing authorisation withdrawals, suspensions, or failure to obtain a marketing authorisation renewal for safety reasons. None of the 141 patients who received Evicel in controlled studies were reported to have been withdrawn due to adverse events.

## **Benefit risk assessment**

### ***Benefits***

Both pivotal studies found that Evicel provided a statistically significant improvement in haemostasis compared with control treatments. These findings are clinically as well as statistically relevant because it is widely accepted in the surgical community that reducing bleeding time in surgery, and with it reduced blood loss, is better for patients.

### ***Risks***

Of 141 patients who received Evicel during clinical trials, a total of three patients died (2.1%). One death was possibly related to the study treatment. No patients were reported to have withdrawn from the pivotal trials due to adverse events after receiving Evicel. Thirty-five patients (24.8%) experienced a total of 47 SAEs, 10 of which were reported to be possibly related to treatment. In patients undergoing retroperitoneal or intra-abdominal surgery there were no significant differences between the groups regarding safety profile. In patients undergoing vascular surgery no statistical analysis of adverse events was reported. Graft thrombosis was seen in several patients who received Evicel during vascular surgery; however, it remains unclear whether this event occurred due to Evicel or was likely to occur in this patient group.

Overall the safety of Evicel seemed to be comparable to the control treatments of Surgicel and manual compression. Both Surgicel and manual compression are widely used in Australia.

### ***Balance***

Several therapeutic options for promoting haemostasis during surgery are currently available to Australian clinicians. Any potential addition to the surgeon's available haemostatic arsenal should be at least as safe and effective as the existing options. Evicel

performed significantly better than two active comparators which are widely used in Australia (Surgicel and manual compression). The superiority of Evicel compared with other remaining options, such as Tisseel, remains to be proven.

The pivotal studies reported that patients undergoing gynaecological, urologic, general or vascular surgery had a statistical improvement in haemostasis after receiving Evicel. The relationship between this improvement and any further clinical benefits (such as quicker recover or reduced length of stay) remains unknown.

Presently, clinicians remain uninformed on the safety and efficacy of Evicel in patients requiring emergency surgery, in children and in pregnant or lactating patients. Additionally, information on long-term effects after receiving Evicel or effects of repeat applications is currently lacking.

The morbidity and mortality associated with inappropriate use of the spray applicator is of concern.<sup>23</sup>

### **Conclusions**

The evaluator considered that in general the benefits of Evicel's are greater than its risks as supportive treatment in gynaecologic, urologic and general surgery for the improvement of haemostasis where standard techniques are insufficient, and as suture support for haemostasis in vascular surgery.

The clinical evaluator recommended that the sponsor considers limiting Evicel's application technique to via dripping only. The safety of the spray applicator is currently unknown and several reported adverse events relating to its use are of concern.<sup>24</sup>

As there may be safety issues relating to Evicel, surgeons should be advised to use this product as an adjunct to prior haemostatic measures, rather than as a front line treatment.

## **V. Pharmacovigilance findings**

### **Risk management plan**

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

### **Safety specification**

The summary of the Ongoing Safety Concerns as specified by the sponsor is shown at Table 23.

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<sup>23</sup> Sponsor comment: "This has been addressed via our risk management plan and relates to spray application of all fibrin sealants and not just Evicel."

<sup>24</sup> Sponsor comment: "This matter has been resolved and both applications; spray and dripping have been approved."

**Table 23: Summary of ongoing safety concerns**

Misuse of the product when sprayed, using high pressure in close proximity to tissue surface and open blood vessels, may lead to gas embolism	<b>Important identified risks</b>
<ul style="list-style-type: none"> <li>▪ Rare occurrence of Hypersensitivity/allergic reactions</li> <li>▪ Isolated occurrence of severe anaphylaxis, especially if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product.</li> <li>▪ Complications related to graft occlusion and/or graft infection and/or thromboembolic events could potentially occur, due to the nature of the product. This should be observed particularly in cases of vascular surgery.</li> <li>▪ Incorrect product application could represent a potential risk. This may include: <ul style="list-style-type: none"> <li>○ Overdosing of the product,</li> <li>○ Application outside the area intended, which could lead to tissue adhesion and associated complications,</li> <li>○ Incorrect mixing of the components, that could lead to a lack of clotting of the product, resulting in lack of efficacy.</li> <li>○ Inadvertent intravascular injection may also occur and could lead to thromboembolic event and DIC, and there is also a risk of anaphylactic reaction.</li> </ul> </li> <li>▪ Antibodies against components of fibrin sealant/haemostatic products may occur rarely.</li> <li>▪ When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infections agents cannot be totally excluded. This applies to unknown or emerging viruses and other pathogens and in particular to non-enveloped viruses such as parvovirus B19.</li> <li>▪ Off label use of the product could also constitute a potential risk.</li> </ul>	<b>Important potential risks</b>
Uncommon or rare adverse reactions may have not been seen because of the small size of population exposed in clinical trials. Experience in a large population is currently missing.	<b>Important missing information</b>

The OPR reviewer noted that 'CNS and peripheral nervous tissue effects' should be included as an Important potential risk. In addition, 'Use in emergency surgery', 'Use in children', 'Use in pregnant or lactating patients' and 'Repeated and/or long-term exposure effects' should be included as Important missing information.

### Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance for most of the potential safety concerns. For the identified risk of 'Complications relating to graft occlusions, graft infection or thromboembolism event in vascular surgery', the post authorisation safety study (PASS) will inform on this issue. This study is a non-interventional observational study in vascular surgery.

It was considered unusual that the sponsor proposed routine pharmacovigilance activities to monitor only the Important potential risks, rather than all the Ongoing Safety Concerns. It was recommended that the sponsor amend the RMP to reflect the latter position, in the format of summary tables required in the EU-RMP template.

In principle there was no objection to the sponsor implementing an additional PASS study to further monitor the important potential risk: 'Complications related to graft occlusions and/or graft infection and/or thromboembolic events, particularly in cases of vascular surgery'. However, only the above description was provided and no protocol for proposed and ongoing studies was provided.

### **Risk minimisation activities**

The sponsor stated that routine risk minimisation activities are thought to be adequate to minimise risks identified in most of the safety concerns. However, it would appear that no such activities are proposed for the specified Important missing information: 'Experience in a large population'.

In relation to the Important identified risk: 'Air embolism' the sponsor has stated that as part of the educational program the surgeons will be instructed on the correct use of the product, including dose and application. This will be achieved by onsite and also hands-on training, where requested. There will also be a warning on the product label and a "Dear Dr" letter alerting to the possibility of air embolism and the proper use of the product.

Additional risk minimisation activities have also been proposed for the specified Important potential risks.

Routine risk minimisation activities should also be applied to the new safety concerns: 'CNS and peripheral nervous tissue effects', 'Use in emergency surgery', 'Use in children', 'Use in pregnant or lactating patients' and 'Repeated and/or long-term exposure effects'.

### **Summary of recommendations**

The OPR reviewer made the following recommendations to the Delegate.

- It is unusual that the sponsor has proposed routine pharmacovigilance activities to monitor only the Important potential risks rather than all the Ongoing Safety Concerns. It was recommended that the sponsor amend the RMP to reflect the latter position, in the format of summary tables required in the EU-RMP template.
- In principle there was no objection to the sponsor implementing an additional PASS study to further monitor the important potential risk: 'Complications related to graft occlusions and/or graft infection and/or thromboembolic events, particularly in cases of vascular surgery'. However, the protocol should be provided and the sponsor should clarify the status of this study as it would appear that it may have already have been initiated. If this study has been completed the results/analysis of this study should be submitted to the TGA for review.
- In addition to the Ongoing Safety Concerns as specified by the sponsor it was recommended that 'CNS and peripheral nervous tissue effects' be included as an Important potential risk and 'Use in emergency surgery', 'Use in children', 'Use in pregnant or lactating patients' and 'Repeated and/or long-term exposure effects' be included as Important missing information. It was also recommended that these new safety concerns be monitored by routine pharmacovigilance activities.
- The clinical evaluator has stated: "This report recommends that additional studies are conducted to inform upon the safety of repeated, long term applications of Evicel." Consequently it was recommended that the sponsor consider conducting such a study and submit to the TGA a draft protocol, including milestones for evaluation and reporting or provide compelling justification as to why no such study is required.
- Routine risk minimisation activities should also be applied to the new safety concerns: 'CNS and peripheral nervous tissue effects', 'Use in emergency surgery', 'Use in

children', 'Use in pregnant or lactating patients' and 'Repeated and/or long-term exposure effects'.

- The sponsor should definitively state whether the proposed additional risk minimisation activities will be conducted in Australia, particularly in regards to a Dear Doctor Letter in relation to the Important identified risk: 'Air embolism' and the Johnson & Johnson Wound Management Professional Educational programs on the use of adjunctive haemostats and sealants that are held several times per year at training facilities throughout Europe.
- The sponsor has not provided any information detailing how the effectiveness of each proposed additional risk minimisation activity as a measure to reduce risk will be assessed. Consequently this aspect of the RMP cannot be assessed. The sponsor should amend the summary table accordingly.
- The reviewer also made recommendations with respect to the proposed PI and CMI but these are beyond the scope of this AusPAR

## VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

### Quality

GMP approvals for a number of sites involved in the manufacture of the product were still outstanding at the time of this Overview.<sup>25</sup> Otherwise there were no objections to registration on quality grounds. The product is prepared from plasma obtained in the USA. All viral/prion safety issues have been satisfactorily addressed.

The application was considered by the Pharmaceutical Subcommittee (PSC) at its January 2011 meeting. No objections to registration were raised. However the subcommittee raised the issue of whether the traceability procedures for the product were adequate in the event of a "look-back" program being instituted. The TGA has not imposed any special requirements for traceability on either of the two currently registered fibrin sealants, other than recommendations in the PI to record patient name and batch number for each use. Any new requirements would need to be applied uniformly for all plasma derived products. *The sponsor was invited to comment on this issue in the pre ACPM response.*

### Nonclinical

The preclinical evaluator has no objections to registration of the product for the proposed indications. However, the evaluator has raised concerns regarding use of the product in neurosurgery.

A study in rabbits in which Evicel was used to seal a lesion in the dura mater, demonstrated that the product produced an intense inflammatory response, with severe and extensive adhesions involving the dura mater, pia mater and other soft tissues. The evaluator stated that the significance and long term consequences of these changes are not clear but that they require further investigation prior to approval of the product for use in neurosurgery. This issue is discussed further below.

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<sup>25</sup> Sponsor comment: "The GMP issue has now been resolved."

## Clinical

### Clinical evaluation

The clinical evaluator recommended approval of the application.

The sponsor provided a response to the clinical evaluation. The evaluator had queried whether the sponsor had provided one additional study to the FDA, which had not been submitted in Australia. A copy of this study was provided, which turned out to be one which had been included in the Australian submission (Study Q-LIV-008).

### Efficacy

#### *Pivotal studies*

The submission included two pivotal randomised controlled trials.

Study 400-05-06 enrolled subjects undergoing intra-abdominal or retroperitoneal procedures, including urological, gynaecological or general surgery. For each subject the surgeon identified intra-operatively a soft tissue target bleeding site (TBS). Subjects were then randomised to treatment with either:

- Evicel applied by dripping or spraying. The dose supplied was 5+5 mL but the surgeon could apply amounts at his or her discretion.
- Surgicel, which is a haemostatic product presented as an absorbable gauze made from cellulose. Surgicel is registered in Australia. The surgeon was supplied with a 10.2 cm x 20.3 cm sheet but could apply additional amounts if required.

The primary endpoint was the percentage of patients with absence of bleeding at the TBS at 10 minutes. Presence or absence of bleeding was determined by the surgeon and hence assessment was not blinded.

- *Non-inferiority* would be concluded in the lower limit of 95% confidence interval for the relative risk of achieving haemostasis (Evicel result ÷ Surgicel result) was above 0.8.
- *Superiority* would be concluded in the lower limit of 95% confidence interval for the relative risk of achieving haemostasis (Evicel result ÷ Surgicel result) was above 1.0.

Results for the primary endpoint are shown in Table 24 (see also Table 5).

**Table 24: Results for the primary endpoint**

	Evicel	Surgicel
% of patients with absence of bleeding at 10 mins	63 / 66 (95.5%)	56/69 (81.2%)
Relative risk of achieving haemostasis at 10 mins	1.18 (95% CI: <b>1.04</b> – 1.36)	

As the lower limit of 95% confidence interval for the relative risk was >1.0, superiority was concluded.

A variety of secondary endpoints (absence of bleeding at 4 and 7 minutes, time to haemostasis, incidence of treatment failure) also favoured the Evicel arm.

Study 400-05-01 enrolled subjects undergoing vascular surgery (end to side arterial anastomosis involving the femoral or an upper extremity artery). Following suture of the graft and release of the arterial clamp, if the surgeon decided that additional haemostatic measures were required, patients were randomised to receive:

- Evicel applied by dripping. The dose supplied was 2+2 mL.



- Manual compression of the anastomotic site with sponges.

The primary endpoint was the percentage of patients with absence of bleeding at the anastomotic site at 4 minutes. Presence or absence of bleeding was determined by the surgeon and hence assessment was not blinded. The study was designed as a superiority trial. Results for the primary endpoint are shown in Table 6.

Secondary endpoints (absence of bleeding at 7 and 10 minutes, incidence of treatment failure) also favoured the Evicel arm, although there was no difference in the incidence of bleeding related complications (anaemia, haematoma, bleeding as an adverse event, increased sanguinous drainage, seroma and ecchymosis).

### **Other studies**

The sponsor included six efficacy studies in the submission which were conducted with a product known as Quixil, a predecessor product to Evicel. The formulation of Quixil differed to that of Evicel in that it contained lower concentrations of clottable proteins and included an antifibrinolytic agent, tranexamic acid. One study was conducted in the vascular surgery setting, two in liver surgery and three in orthopaedic surgery. As the formulation of Quixil differs from that of Evicel, the efficacy data from these studies cannot be considered directly relevant.

### **Safety**

In the two pivotal studies, a total of approximately 140 subjects were treated with Evicel. All subjects received a single administration. Application to multiple sites during a single procedure or repeat use during subsequent surgical procedures, were not studied.

In Study 400-05-06, the overall incidence of adverse events was comparable between the Evicel and Surgicel groups. In the Evicel arm there was a slightly lower incidence of serious adverse events (17.9% versus 22.1%) and severe events (9.0% versus 14.7%) (Table 14). Very few of the events were considered related to the products used. The incidence of individual adverse events was broadly comparable between the two groups (Table 15).

In Study 400-05-01, the overall incidence of adverse events was comparable between the Evicel and manual compression groups (Table 16). There was an excess of *related* adverse events in the Evicel group (12% versus 0%). This was explained by the sponsor as being due to study investigators not ascribing any adverse events in the comparator group as being due to manual compression, as this was considered to be a standard part of the surgical procedure. The incidence of individual adverse events was broadly comparable between the two groups (Table 17). The incidence of graft occlusion/thrombosis was comparable (8 patients in each group).

There were a further eight studies in the submission conducted with the Quixil product that contained safety data. In comparative studies, the adverse event profile of Quixil was generally similar to that seen in the comparator groups. No additional safety concerns were raised.

The Quixil product has been approved in Europe since 1999 and the USA since 2001. The Evicel product has been registered in Europe since 2008 and in the USA since 2006. Two significant safety issues have been identified from the postmarketing data:

- Cases of air embolism have been reported when Evicel is delivered via a spray applicator. Similar cases have been reported with other fibrin haemostatic agents/sealants. These adverse events are related to improper use of the spray device rather than any toxicity of the fibrin product.
- Three cases of death have been reported in which the Quixil product came into contact with the dura mater during CNS surgery. It appears that these cases may have been

suspected to be due to neurotoxicity of the tranexamic acid contained in the Quixil product, as a warning to this effect was added to the prescribing information. The TGA adopted EU guideline also contains the following statement:

*“Fibrin sealants used in neurosurgery should not contain tranexamic acid, since cerebral oedema and seizures have occurred.”*

No such cases have been reported with Evicel and a warning against use in neurosurgery has not been included in the European prescribing information for Evicel. The sponsor considered that two of these deaths may have been due to malignant hyperpyrexia syndrome associated with anaesthetic agents.

### **Risk management plan**

At the time of this Overview, there were still some outstanding issues with the proposed RMP as outlined in the evaluations performed by the TGA’s Office of Product Review. These will require some further negotiation prior to approval but should not prevent registration.

### **Risk-benefit analysis**

#### **Delegate considerations**

##### ***Use via spray applicator***

The clinical evaluator raised concerns about the safety of spray application of the product due to cases of air embolism and has suggested that the product should only be approved for use by dripping. The air embolism issue is related to inappropriate use of the spray application device rather than any property of the fibrin product.

Given that the TGA has approved spray application of Artiss and the safety issue is not directly related to the fibrin sealant, the Delegate did not consider it would be reasonable to reject spray application on safety grounds. The safety issue could be addressed through the product information and any training programs for surgeons run by the sponsor.

##### ***Use in neurosurgery***

The nonclinical data raised concerns regarding the safety of Evicel when used to seal the dura mater in neurosurgery. The nonclinical evaluator had initially recommended that consideration be given to contraindicating the product for use in neurosurgery. Following the provision of further data in dogs the evaluator no longer recommended a contraindication. A clinical trial of Evicel used in the sealing of the dura mater is underway and is expected to be completed in 2012. Until such time as the results of this trial are available, the Delegate considered that a specific precautionary statement against use in neurosurgery should be included in the PI.

#### ***Assessment of risks and benefits***

Efficacy of the product has been demonstrated in two randomised, controlled trials. With the possible exception of safety in neurosurgery, no specific safety concerns were raised by the submitted data. The Delegate considered that the risk benefit ratio of the product was favourable and proposed to approve the application.

### **Response from sponsor**

The sponsor agreed with the indication recommended by the Delegate, namely a general surgical haemostasis indication for situations in which standard surgical techniques are

insufficient and for use as suture support in vascular surgery. The sponsor addressed issues raised by the Delegate.

### ***Traceability***

The requirement for recommendations in the PI to record the batch number for each use was acceptable. On the other hand, the requirement for recommendations in the PI to record patient name for each use is contradicting the sponsor's patient's confidentiality policy. However, the exact destination of each batch shipped from the sponsor is recorded in the sponsor files. It is up to the discretion of the clinician and the hospital to define the procedures and keep a track record of the batch numbers being used for each procedure/patient. The sponsor cannot reinforce this.

### ***Use of the product in neurosurgery***

The sponsor agreed with TGA that adequate data to obtain an indication for sealing was not yet available for Evicel. Therefore, the use of the product for dura sealing following neurosurgery is not in the intended indication. In the absence of a Neuroindication for Evicel, the sponsor believed that no precautionary statement is required to be added to the PI. However, the sponsor accepts the addition of the following in the PI:

“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”.

### ***Safety issue regarding air embolism***

The sponsor indicated that the air embolism concern is thoroughly addressed in the DDL (Dear Doctor Letter) and the PSUR. The Risk Management Plan (RMP) for Evicel has also been revised to include the risk of air embolism associated with the use of pressurised air when applying the fibrin sealant. The spray pressure and distance to be followed are to be provided within the product instructions.

### **Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

#### ***Efficacy and safety***

The ACPM agreed with the Delegate that the submission provided sufficient evidence of efficacy and safety. The ACPM noted the increased risk of thromboembolic complications in small vessel closure and the possibility of air embolism when the spray applicator is used inappropriately. Monitoring of the device and of the gas pressure is necessary.

#### ***Indication***

The ACPM considered this product to have a positive benefit risk profile for the indication of:

*As supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.*

*As suture support for haemostasis in large vessel vascular surgery.*

The ACPM also made recommendations with respect to the PI and CMI but these are beyond the scope of this AusPAR.

The ACPM advised that the implementation by the sponsor of the recommendations to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Evicel would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Evicel solutions for fibrin sealant, 4 mL (comprising fibrinogen solution 2 mL vial and thrombin solution 2 mL vial) and Evicel solutions for fibrin sealant, 10 mL (comprising fibrinogen solution 5 mL vial and thrombin solution 5 mL vial), indicated for:

- *As supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.*
- *As suture support for haemostasis in large vessel vascular surgery.*

### ***The following specific conditions apply to these therapeutic goods***

1. The EU Risk Management Plan Version: 7, dated 13 June 2012, to be revised as specified in the sponsor's correspondence dated 10 September 2012 in the form of an Australian Specific Annex as agreed to in the sponsor's correspondence dated 19 September 2012, must be implemented.
2. Batch Release Testing by the TGA:

It is a condition of registration that all independent batches of;

- Evicel solutions for fibrin sealant 4 mL (thrombin 2 mL, fibrinogen 2 mL) vials (AustR 181318)
- Evicel solutions for fibrin sealant 10 mL (thrombin 5mL, fibrinogen 5 mL) vials (AustR 181319)

imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

## Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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## **Therapeutic Goods Administration**

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Reference/Publication #