



European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/CHMP/449199/2008

ASSESSMENT REPORT

FOR

Evicel

Common Name: human fibrinogen / human thrombin

Procedure No. EMEA/H/C/000898

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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Medicinal product no longer authorised

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant OMRIX biopharmaceuticals S.A. submitted on 25 July 2007 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Evicel, through the centralised procedure under Article 3 (2) b of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23-26 January 2006. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was on the basis that it is a new medicinal product derived from human plasma: The formulation of the fibrin sealant kit is novel in that its fibrinogen component is not formulated with any antifibrinolytic agent (such as aprotinin or tranexamic acid).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:

Composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Licensing status:

Evicel has been given a Marketing Authorisation in USA on 06.06.2006.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Dr. **Christian K. Schneider**

Co-Rapporteur: Prof. **Michal Pirozynski**

1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 25 July 2007.
- The procedure started on 15 August 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 November 2007.
- During the meeting on 10-13 December 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 13 December 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 March 2008.
- The summary report of the inspection carried out at the following site(s) Omrix Biopharmaceuticals Ltd., Kiryat Ono, Israel between 13-17 April 2008 was issued on 10 July 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13 May 2008.
- During the CHMP meeting on 27-30 May 2008 the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 June 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 July 2008.
- During the meeting on 21-24 July 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Evicel on 24 July 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 July 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Evicel is a fibrin sealant kit consisting of two human plasma-derived components, Human Fibrinogen and Human Thrombin.

The term fibrin sealant denotes a product containing coagulation factors, to be administered topically in order to produce a fibrin clot. Typical fibrin sealant kits consist of at least two components, which are kept separately until allowed to mix in topical application. One of the components usually contains human fibrinogen, as substrate of the clot. The other component contains biologically active thrombin, which will convert the fibrinogen of the first component to fibrin.

Fibrinogen is cleaved to fibrin by thrombin, and consequently the fibrin clot is formed. Factor XIII (contained in low amounts in the preparation) crosslinks fibrin fibers, after activation to Factor XIIIa by thrombin. By this mechanism haemostasis is achieved and a matrix generated, which supports the natural wound healing process. The final stage of the blood coagulation process, i.e. the natural mechanism of clot formation, is imitated by fibrin sealant.

Evicel is a further development of Quixil, which is approved for marketing in 14 EU countries since 2003, first in 1999 in UK. One difference between Evicel and Quixil is the final composition of the fibrinogen component whereas the thrombin component remains the same. The fibrinogen component of Quixil contains the synthetic antifibrinolytic agent tranexamic acid (TA), which inhibits the degradation of fibrinogen. However, because tranexamic acid is potentially neurotoxic Quixil is contraindicated for use in neurosurgery and all procedures where contact with the CSF and dura mater might occur. By specific removal of plasminogen the need for stabilization with tranexamic acid is avoided, and Evicel's fibrinogen is formulated without tranexamic acid. Its protein concentration is 30-50% higher requiring the submission of a new application for marketing authorisation.

The indication claimed by the applicant is "Evicel is intended for clinical use as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis and to promote sealing, or as suture support for haemostasis in vascular surgery". The approved indication is "Evicel is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. Evicel is also indicated as suture support for haemostasis in vascular surgery". Evicel is intended for episodic use only. The posology should always be oriented towards the underlying clinical needs of the patient. In clinical trials in vascular surgery, the individual dosage used was up to 4 ml, whereas in retroperitoneal or intra-abdominal surgery the individual dosage used was up to 10 ml, however application of the product must be individualised by the treating physician.

2.2 Quality aspects

Introduction

Evicel Solutions for Sealant is a Fibrin Sealant Kit (Ph. Eur. 01/2005:0903) consisting of two biological, double virus-inactivated components, Human Fibrinogen and Human Thrombin, each supplied as frozen solution with an application device. Upon thawing component 1 is to be mixed with component 2 in equal volumes. Human Fibrinogen is a concentrate of clottable protein and Thrombin is an enzyme that causes clottable protein to coagulate. Thus, when the two components are mixed together they immediately form a fibrin clot. Evicel is intended for episodic use in a surgical context.

Component 1 - Human Fibrinogen

The primary difference between the Fibrinogen components of Quixil and Evicel, is that plasminogen is removed from the preparation by an affinity chromatography, so that the need to add tranexamic acid as a stabiliser is avoided. Tranexamic acid serves as a competitive inhibitor of plasminogen, and is used in Quixil as an anti-fibrinolytic agent. However, tranexamic acid is potentially neurotoxic, and

as a result, Quixil is contraindicated for use in neurosurgery and procedures where contact with the CSF and dura mater might occur.

All the earlier manufacturing steps, including the viral inactivation, are identical to those in manufacture of Quixil's Human Fibrinogen component. The concentration of protein in the fibrinogen component of Evicel is 30-50% higher than in the Quixil component.

Composition

Human Fibrinogen component is a non-pyrogenic solution, pH 6.8 – 7.2, consisting of a concentrate of clottable proteins with a concentration of 50-90 mg/ml. It principally consists of fibrinogen, but also of fibronectin, albumin, immune globulins and trace amounts of other plasma proteins (e.g. Factor VIII, Factor XIII, von Willebrand Factor). In addition, it contains arginine hydrochloride as stabiliser as well as glycine, sodium chloride, sodium citrate and calcium chloride as buffer agents. Human Fibrinogen component is supplied to the user as frozen solution.

Container and closure

Human Fibrinogen drug product is filled in 5 ml aliquots into 10ml Ph.Eur. Type I glass vials; or 1ml or 2ml aliquots into 7ml vials. Rubber infusion stoppers of type I (Ph.Eur., Rubber Closures for Containers for Aqueous Preparations for Parenteral Use) are used as closures for the vials. Both vials and stoppers are siliconised. The closures are sealed in place with aluminium crimps with flip-off caps. The specifications of the glass vials and the infusion stoppers as well as the corresponding Quality Certificates are provided. In summary, the container closure system for Human Fibrinogen drug product is in compliance with Ph.Eur. requirements.

Drug Substance

Manufacturing process development

The manufacturing process development is sufficiently described. The rationale for the introduction of the affinity chromatography for selective removal of plasminogen is sufficiently justified. By specific removal of plasminogen the need for stabilization with tranexamic acid is avoided, and Evicel's Fibrinogen is formulated without tranexamic acid. Some of the validation and developmental studies were conducted on batches of Human Fibrinogen for Quixil. However, all steps up to (and including) the pasteurization are identical, and all development and validation studies of these steps are equally applicable to Evicel's Fibrinogen. For the steps that differ, relevant development and validation studies have been performed. A second modification of the manufacturing process was a scale-up of production by 3.5 fold.

Starting material

Human plasma is used as starting material for the production of fibrinogen. The collection, viral marker testing, transport and storage of single donations as well as the viral marker testing of the plasma pool are documented in the PMF which is evaluated and certified in parallel to the centralised procedure for Evicel (EMA/H/PMF/000013/07).

Description of manufacturing process

The manufacturing process of the fibrinogen component is described in detail and comprehensively. It consists of precipitation and purification steps and includes two steps for virus inactivation.

In-process controls

The applicant has established in-process-controls and defined acceptance criteria at critical steps of the manufacturing process to assure that the process is controlled. A rationale is given for all in-process controls supported by experimental data from 21 human fibrinogen batches. The in-process controls performed during manufacture of human fibrinogen bulk are appropriate to ensure the quality and consistency of the drug substance.

Batch size

The batch size for the production of fibrinogen drug substance is adequately defined. The only step where pooling of intermediates may take place is at the cryoprecipitation level.

Reprocessing

In case of a mechanical failure of the centrifugation, filtration, or chromatography systems, the repetition of the processing step would be permitted, provided that the manufacturer's Quality Assurance department confirms that this repetition is unlikely to affect the quality of the product. The repetition of the virus inactivation is not allowed and the drug substance is not reworked.

Control of materials

Certificates of Analysis are provided for all ingredients, reagents and auxiliary material purchased and retested by the manufacturer according to Ph. Eur. in the manufacture of drug substance fibrinogen. In the case where there is no pharmacopoeial specification, the supplier's specifications are provided. Water for injection for production is manufactured and controlled by the manufacturer's PFI.

Intermediates

Cryoprecipitate used as intermediate for the production of fibrinogen is produced from human plasma which collection, testing, storage and transport is documented and evaluated within the OMRIX PMF certification procedure ((EMA/H/PMF/000013/07).

Analytical data from cryoprecipitate used for the production of 3 batches of fibrinogen were submitted for characterisation of cryoprecipitate.

The storage of the cryoprecipitate intermediate is justified by stability data.

Process validation

Manufacturing steps critical for safety and quality of fibrinogen drug substance were identified and adequately validated based on data from three commercial scale validation batches. In addition, data from the analysis of final product from the validation batches as well as in-process control data from 21 batches produced in 2006 were provided. In conclusion, the manufacturing process is sufficiently controlled to ensure batch to batch consistency.

- Specification

Appropriate drug substance specifications are set for Human Fibrinogen and are sufficiently justified.

Analytical procedures

The analytical methods used for the control testing of the fibrinogen drug substance are adequately described and validated.

Assay for fibrinogen

Initially, the applicant applied for a modified version of the clottable protein test for determining the active substance in the fibrinogen component and called this assay clottable fibrinogen test. However, as there was a statistically significant difference between this test and the Ph. Eur. test, the applicant agreed within the response to the List of outstanding Issues to measure potency of fibrinogen by "Determination of Clottable Protein" as specified by Ph. Eur. monograph for Fibrin Sealant Kit (01/2008:0903) with the modification that the determination of protein will be done by a method which compares the UV absorbance at 280 nm of the test sample with that of a standard protein solution. A batch of Human Fibrinogen, calibrated for total protein is used as the standard. The proposed method has been compared with the Ph. Eur. method (Kjeldahl method). Statistical evaluation revealed no statistically significant differences between the two methods.

The active ingredient of the Fibrinogen component will be declared as "Clottable Protein". The specification is 50-90 mg/ml (71 % to 129 %) corresponding to the specification range defined by the Ph. Eur.

- Stability

The provided stability data support the storage of Human Fibrinogen drug substance.

- Comparability Exercise for Fibrinogen Drug Substance of Quixil vs Evicel

For comparison the applicant provided the composition of Human Fibrinogen of Quixil versus Evicel.

Drug Product

- Pharmaceutical Development

By specific removal of the product related impurity plasminogen during the purification process of the fibrinogen drug substance of Evicel (see above) the need for stabilisation of fibrinogen with tranexamic acid is not required. The excipients used for formulation are non-toxic and act as stabilising agents. They are also contained in the formulation of the predecessor product Quixil.

Description of the manufacturing process

The manufacturing process of the Human Fibrinogen drug product is adequately described.

The batch formula has been provided. Critical process steps were identified and validated at commercial scale to ensure batch to batch consistency.

Control of excipients

All excipients are already present at their final concentration in the drug substance and are adequately controlled.

- Product Specification

The specifications for the Human Fibrinogen drug product are adequately set and justified.

Analytical methods are appropriate to control the defined parameters and comply with the Ph.Eur monograph. Validations of analytical methods were provided according to ICH guideline Q2 (R1).

The Ph.Eur. requires that in case a Human Fibrinogen drug product contains factor XIII at a concentration exceeding 10 U/ml, its estimated potency should appear on the label. The applicant does not consider factor XIII to be an active ingredient in the Human Fibrinogen component of Evicel.

- Stability of the Product

The provided stability data justify the shelf life and storage conditions as described in the SPC.

In use stability data support the wording of the SPC (section 6.6) that the incubation period at 37°C for thawing of Evicel's frozen Fibrinogen component is defined to not more than 10 minutes.

Component 2 – Human Thrombin

Introduction

Thrombin belongs to the family of Trypsin-like serine proteases which are synthesized as inactive precursor to be cleaved by limited proteolysis into the active form. In the manufacture of Evicel's Human Thrombin, Prothrombin is cleaved and released as Thrombin during a chromatographic purification step. Thrombin is a highly specific protease which cleaves fibrinogen into fibrin. Thrombin (α thrombin) is subject to slow auto-degradation to the smaller proteins, β - and γ -thrombin.

The manufacture of Human Thrombin starts with cryopoor plasma followed by purification steps using anion and cation exchange chromatography. The applicant claims that no manufacturing changes occur in Evicel's Thrombin component compared to the predecessor product Quixil.

Composition

Evicel's Thrombin component is a non-pyrogenic solution consisting of 800-1200 IU/ml human thrombin with human albumin and mannitol as stabilisers and as well as calcium chloride and sodium

acetate as buffer agents. The pH of the solution is 6.8 – 7.2. Thrombin component is supplied to the user as frozen solution.

Container closure system

The container closure system for Human Thrombin is the same as for Human Fibrinogen.

Drug Substance

Human Thrombin drug substance is defined as the formulated bulk prior to sterile filtration and filling into vials.

Manufacturing process development

A summary of pharmaceutical development studies performed to optimize and validate the critical steps of the manufacturing process are provided.

Starting material

The human plasma used as starting material for the production of Human Thrombin is the same as the one used for the production of Human Fibrinogen. The collection, viral marker testing, transport and storage of single donations as well as the viral marker testing of the plasma pool are documented in the PMF which is evaluated and certified in parallel to the centralised procedure for Evicel (EMA/H/PMF/000013/07).

Description of the manufacturing process

The applicant has provided extensive information to adequately describe the manufacturing process and process controls. It consists of purification steps and two steps for virus inactivation/removal.

In-process controls

Adequate in-process controls and acceptance criteria are established at critical steps to ensure that the manufacturing process is sufficiently controlled.

Batch size

The batch size is defined.

Reprocessing

The criteria for reprocessing are the same as for the manufacture of Human Fibrinogen.

Control of materials

Certificates of Analysis are provided for all ingredients, reagents and auxiliary material purchased and retested by the manufacturer according to Ph. Eur. in the manufacture of drug substance. In the case where there is no pharmacopoeial specification, the supplier's specifications are provided. Water for injection for production is manufactured and controlled by the manufacturer's PFI.

Albumin

Human Thrombin component contains Human Albumin for stabilisation. It complies with the Ph. Eur. monograph "Human Albumin Solution".

The information related to the plasma used as starting material in the manufacture of Albumin is provided in a Plasma Master File, which is certified. This PMF is valid to its full extent for Human Albumin.

Certificate of Analysis for Human Albumin has been provided. The applicant confirms to use the albumin only when it is within its shelf life. EU OMCL batch release testing of the albumin is performed.

Intermediates

There is no pooling of intermediates during the production of Human Thrombin drug substance.

Process validation

The consistency and robustness of the manufacturing process used for production of Human Thrombin was validated by the manufacture of three consecutive batches. Critical manufacturing steps were identified and adequately validated. In addition, in-process controls of the three validation batches and batches manufactured in 2006 were analysed. All results were within the specified limits demonstrating the batch to batch consistency of drug substance production. In line with this finding were the results from testing and additional characterisation of the finished product of the validation batches.

- Specification

Adequate specifications are set for the Human Thrombin drug substance and sufficiently justified.

Analytical procedures for the testing of the Human Thrombin drug substance are submitted. Thrombin is determined by the clotting assay described for Component 2 of Fibrin sealant Kit in the Ph.Eur.. In compliance with ICH guideline Q2(R1) (Validation of Analytical Procedures: Text and Methodology) the applicant has provided method validations for all analytical methods used in the quality control during release of Human Thrombin drug substance. For analytical procedures which are not fully compendial, a justification was provided why comparability could not be fully shown between the Ph.Eur. method and the method used.

Batch analysis

Batch results from 5 successive batches of Human Thrombin drug substance were submitted. All test results are within the defined specifications and demonstrate the consistency in the manufacture of Human Thrombin component of Evicel.

Container closure

Human Thrombin drug substance is filled in bags. The contact layer is Polyethylene-vinyl acetate Ph. Eur. The bags are sterilised by gamma-radiation.

- Stability

Human Thrombin drug substance may be stored. For justification sufficient stability data were provided.

Drug Product

- Manufacture of the Product

Description of manufacturing process

Sufficient information has been provided to adequately describe the manufacturing process of Human Thrombin drug product.

The batch formula is given. The process has been sufficiently validated for this production scale. Critical parameters at critical steps of the drug product manufacturing process were identified to assure that the process is controlled to ensure the quality and consistency of the drug product.

Control of excipients

All excipients are already present at their final concentration in the drug substance and are adequately controlled.

- Product Specification

The Human Thrombin drug product specifications are adequately set and justified to ensure product quality.

The analytical methods are appropriate to control the defined parameters and comply with the Ph.Eur monograph. Validations of analytical methods were provided according to ICH guideline Q2 (R1).

Batch analysis

Analysis of data from five representative batches demonstrates consistent batch to batch quality of Human Thrombin drug product.

- Stability of the Product

The provided stability data justify the shelf life and storage conditions as described in the SPC.

Evicel - Assembled Product

Description and Composition

Evicel is a fibrin sealant consisting of two plasma-derived components, Human Fibrinogen and Human Thrombin solutions. These are supplied in the frozen state, thawed by the user, and combined for local application with a CE marked application device to achieve haemostasis. The composition of the two components is given above. The application device is not part of this application for marketing authorisation.

Container

The Evicel kit consists of two cardboard packages. One package contains one vial of each of the biological components, Human Fibrinogen and Human Thrombin and the other contains the CE-marked application device.

- Manufacture

Description of the manufacturing process

A package of Evicel contains one vial of Component 1 - Human Fibrinogen and one vial of Component 2 – Human Thrombin (each 5ml, 2ml or 1ml) and a CE-marked application device (5ml or 1ml/2ml).

The manufacturing steps include the final packaging of the biological components and QA approval, release storage, assembly and labeling of device package.

- Product Specification

An identification test is performed for the fibrin sealant kit to check whether the two components form a clot immediately when mixed and applied with the device to a glass plate. The performance of the application device in producing a homogeneous mixture of the two components has been validated.

- Adventitious Agents

Both components of Evicel, Human Fibrinogen and Human Thrombin, as well as the Human Albumin used as stabiliser for the thrombin are produced from human plasma sourced in the USA.

Risk of contamination with TSE

Appropriate donor selection criteria are in place. Donors with an increased risk for sporadic or variant Creutzfeldt-Jakob-Disease are excluded. Systems are in place which allow traceability of each donation supplied for the manufacture of fibrinogen, thrombin and albumin in case a donor develops (or is strongly suspected to have developed) vCJD. In this case any batches of Evicel which include suspected donations would be withdrawn from the market and the competent authorities informed.

The prion removal capacity of the manufacturing processes for fibrinogen, thrombin and albumin was investigated. In summary, compliance with Position Statement CPMP/BWP/2879/02 on human TSEs and plasma-derived medicinal products has been demonstrated.

Adventitious viruses

Human Fibrinogen and Human Thrombin

The overall viral safety strategy includes selection of qualified donors and testing of plasma donations collected in the USA. The donor selection and plasma donation testing strategy for viral markers is considered adequate.

The applicant validated virus inactivation steps included in the manufacture of fibrinogen and thrombin. These steps were validated for their capacity to inactivate/remove viruses. The selection of process steps for validation is considered sufficient. The virus studies are of good quality and comply with the requirements of Guideline CPMP/BWP/268/95. Adequate controls (cytotoxicity, interference) were performed and complete study reports including raw data were submitted.

In summary, two dedicated steps for virus inactivation/removal were introduced into the manufacture of fibrinogen. Enveloped viruses are efficiently inactivated at both virus inactivation steps. One of them also inactivates non-enveloped viruses such as Hepatitis A virus. Nevertheless, validation of enveloped virus reduction at pasteurisation should include a Herpesvirus (e.g. PRV). Having a full validation data base is highly recommended for cases when post donation information indicating virus positive samples entering the fractionation pool, would become available. Since there are no general concerns regarding enveloped virus safety this virus validation study can be performed post-authorisation. Since PRV is widely used for this purpose, the manufacturer commits to perform a viral inactivation study with PRV.

The virus reduction strategy for thrombin is based on an efficient inactivation step for enveloped viruses and a step for which removal of enveloped viruses as well as small non-enveloped viruses such as parvoviruses was demonstrated.

Human Albumin

As for fibrinogen and thrombin, the overall viral safety strategy includes selection of qualified donors and testing of plasma donations collected in the USA. The donor selection and plasma donation testing strategy for viral markers is considered adequate.

Due to the established and validated manufacturing procedure and final pasteurisation step, the viral risk from albumin has been adequately minimised.

Risk assessment and Statements in SPC Section 4.4

A risk Assessment according to new chapter 6 of Guideline CPMP/BWP/269/95 concerning HIV, HBV, and HCV has been submitted. The provided data justify the inclusion of the following warning statement into section 4.4 of the SPC:

The measures taken are considered effective for enveloped viruses such as HIV, HBV, HCV, and HAV.

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substances and drug products of both components of Evicel, Human Fibrinogen and Human Thrombin were presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. Safety with regard to transmissible agents, such as human TSE and enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

At the time of the CPMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.

2.3 Non-clinical aspects

Introduction

The non-clinical study program for Evicel focussed on the evaluation of its primary pharmacological effects especially haemostatic efficacy, the frequency of occurrence of post-surgical adhesions and the stability of the clot once formed, in comparison with other marketed fibrin sealants (Quixil, Surgicel, Tissucol and Tisseel).

The pivotal non-clinical studies for Evicel have been conducted in compliance with Good Laboratory Practice (GLP) standards. Most of the other non-clinical studies provided were not performed under GLP standards.

Pharmacology

The pharmacological studies provided are summarised in Table 1:

Table 1: Pharmacological studies performed for Evicel

Study type	Route/Administration	GLP-compliance
Rabbit partial hepatectomy model	Local / sprayed onto resected liver	yes
Rat kidney haemorrhage model	Local / sprayed onto resected kidney	no
Rat kidney haemorrhage model	Local / sprayed onto resected kidney	no
Rat abdominal wall defect model	Local / sprayed onto incised abdominal wall	no

- Primary pharmacodynamics

The primary objective of a rat kidney haemorrhage study was to assess the haemostatic profile of Evicel and secondly to investigate the influence on its haemostatic performance, when different amounts of Fibrinogen degradation products (FgDPs) were added. The impact of the reduction in the clottable Fibrinogen concentration by spiking with Albumin was also investigated. The endpoints measured (occurrence of points of high pressure = bubbles under the clot) were found to be comparable for Evicel and Quixil. When either Albumin or FgDPs were added to Evicel's Fibrinogen component haemostatic properties were found to be weaker.

In a second rat kidney haemorrhage study, two groups each consisting of 10 male rats were either treated with Evicel or with Quixil. Assessment of the haemostatic performance of Evicel when compared to Quixil revealed that clot performed was similar. In both groups, all 10 animals completed and localised points of higher pressure appeared at the clot surface in 2/10 animals in each group.

The goal of the rat abdominal wall incision study was to evaluate the *in vivo* longevity of a clot formed by the Evicel in comparison to other fibrin sealants. A 2cm x 1cm flap in the abdominal wall was made, creating a defect that penetrates the wall muscles. The wounds were sprayed with 1ml of the fibrin sealant preparations, followed by closure of incision and skin. 5 groups of 10 animals each of male rats were used to test Evicel (two groups), Quixil, Tissucol and Tisseel. The animals were sacrificed at several time points up to 14 days following treatment. The results of this study demonstrate comparability in clot longevity within the treatment groups.

The objective of the rabbit partial hepatectomy study was to evaluate the haemostatic properties of two batches of Evicel using a rabbit partial hepatectomy model. The batches differed in the source of cryoprecipitate. Partial hepatectomy was performed in three groups of 10 animals. Each wound was sprayed with at least 1 ml of either the test or the reference fibrin sealants. Time to achieve haemostasis was recorded for each animal following application of the fibrin sealant. The mean time

to haemostasis (ca. 50 s) has been found to be similar within the treated group as well as the amount of fibrin sealant used.

- Secondary pharmacodynamics

Studies have not been submitted.

- Safety pharmacology programme

Studies have not been submitted.

- Pharmacodynamic drug interactions

Studies have not been submitted.

Pharmacokinetics

The pharmacokinetics of α -thrombin was examined in two studies using radio-labelled thrombin, which examined intravenous injection and topical application to cut surface of liver in rabbits.

- Absorption-Bioavailability

Absorption of $^{125}\text{I}\alpha$ thrombin either after intravenous injection or on hepatic wounds in the rabbit was evaluated. The study was performed in randomized comparative designs in which animals received the test material after application to the cut surface or i.v. injection. The results obtained showed that the pharmacokinetic profile in the rabbit was equivalent to that seen in humans after i.v. injection. The C_{max} (7-9 $\mu\text{g}/\text{ml}$) was reached after 45 – 60 minutes after application and the clearance was rapid about, 0.5 $\mu\text{g}/\text{ml}$ remained after 10 hours and levels were almost undetectable after 24 hours.

The study demonstrated that the absorption of $^{125}\text{I}\alpha$ thrombin is rapid and consists mainly of biologically inactive peptides resulting from degradation by plasmin of α thrombin embedded in a clot.

A second study addressed the absorption of ^{125}I -thrombin and ^3H -tranexamic acid after application on hepatic wounds in rabbit. The objective of this study was to evaluate blood levels of ^{125}I -thrombin and ^3H -tranexamic acid after application to the hepatic wounds in rabbit animal model. All animals showed a similar pattern: up to 6 – 10 hours the curves of plasma and filter concentration are parallel, with plasma concentration approximately half of the filter concentrations. After 6 hours the filter concentration tended to increase, decrease or remain the same, while the plasma concentration continue to increase up to 20 hours. The C_{max} of thrombin related proteins was in 55 – 150 mU/ml .

- Distribution

Studies have not been submitted.

- Metabolism

Studies have not been submitted.

- Excretion

Studies have not been submitted.

- Pharmacokinetic drug interactions

Studies have not been submitted.

- Other pharmacokinetics studies

TnBP and Triton X-100

The pharmacokinetics of TnBP and Triton X-100 (1+5) were studied in Sprague – Dawley rats after a single intravenous administration of the compounds. A literature search allowed to state that studies on Nonoxynol-9 substance closely related to Triton x-100 indicated that this substance is excreted primarily via the liver – bile route in the faeces and secondarily in the urine. The half life is several days. Intravenous administration of ¹⁴C-labeled Naonoxynol-9 resulted in complete metabolism of the compound, with tissue distribution that concentrated on small and large intestines.

A number of studies address the potential neurotoxicity and immunotoxicity of TnBP and Triton X-100. When a LD₅₀ (1863 mg/kg) was given to adult hens, there were no demonstrable signs of neural damage or other significant clinical findings. Administration of doses exceeding (over 9000 times) the daily dose of Evicel gave no indication of any effect on primary or secondary anti-SRBC (sheep red blood cell) response, leukocyte counts, or the sizes of vital organs (kidneys, heart, lungs, and thymuses). Serum IgG and IgM were also similar to that of controls.

The potential cytotoxic effects on the fibroblasts have been addressed. Triton X-100 proved to be toxic in the 25µg/mL area; however this was reduced when the serum protein increased. There was no evidence of significant cell damage in the mutagenicity studies.

Triton X-100 inhibits enzyme cell activity in a cell free system. The LC50 for cytochrome oxidase fell within the 22 ppm range. Rapid dilution of the residual amounts of Triton X-100 infused with plasma and immunoglobulin allows concluding that these in vitro findings have no toxicological consequences.

Toxicology

- Single dose toxicity

Single dose toxicology studies were performed in full conformity with GLP regulations. Table 2 summarises studies performed with TnBP and Triton X.

Table 2: Single dose studies

Substance tested	species	route	Dose administered (mg/kg bw)
TnBP+ Triton X-100 (1+5)	rat	i.v.	3.16 - 100
TnBP+ Triton X-100 (1+20)	Mouse	i.p.	1.56 – 22.8
	rat	i.p.	0.49 – 33.5
TnBP + Triton X -100 (1+5)	Rat mature	i.p.	21.5 – 316.0
	Rat newborn	i.p.	10.0 – 316.0

Results of single dose studies of TnBP and Triton X – 100 administration shows LD50 values ranging from 5.1 ± 25.5 to 35 ± 177 mg /kg. This depended on the rodent species and route of administration. This is at least 3000 times greater than the dose of TnBP and Triton X-100 expected in humans receiving Evicel. The LLD (lowest lethal dose) ranges from 5.3 ± 26 to 6.1 ± 122 mg/kg. The NOAEL (no adverse effect level) was 0.2 ± 4 to 7.7 ± 39 mg/kg at least 130 fold greater than the calculated dose for patients.

- Repeat dose toxicity (with toxicokinetics)

The combination of TnBP and Triton X – 100 in a mixture ratio of 1 + 5 was tested in rats and dogs for 13 weeks by means of intravenous administration, to mimic the route of administration in humans (see Table 3).

Table 3: Repeat dose toxicity studies

Substance tested	species	route	Doses administered ($\mu\text{g/kg/bw/day}$)	
			TnBP	Triton X - 100
TnBP + Triton X-100 (1+5)	rat	i.v.	12	60
			60	300
			300	1500
	dog	i.v.	13	65
			50	250
			500	2500

The calculated NOAEL for local effects was $12 \pm 60 \mu\text{g/kg}$ in the rat, and $13 \pm 65 \mu\text{g/kg}$ in the dog. NOAEL for systemic effects was $300 \pm 1500 \mu\text{g/kg}$ for rat and $500 \pm 2500 \mu\text{g/kg}$ for dog. These values being at least 200 fold greater than the calculated exposure to patients.

- Genotoxicity

The mutagenic potential of fibrinogen and thrombin and the combination of TnBP and Triton X-100 has been assessed using the Ames test, mammalian mutagenicity assay (V79 cells) or chromosomal analysis of bone marrow in Sprague Dawley rats and the micronucleus test in Sprague Dawley rats and NMRI mice (see Table 4).

Table 4: Genotoxicity Studies performed fibrinogen and thrombin and the combination of TnBP and Triton X-100.

Substance tested	Type of study	Species/test	route	Doses administered	
thrombin	Gene mutation test	Reverse mutation tests with <i>Salmonella typhimurium</i> (with and without metabolic activation) Prokaryocytes	In vitro	5000; 1600; 512; 164; 52 $\mu\text{g/plate}$ 5000; 2800; 1568; 878; 492 $\mu\text{g/plate}$	
fibrinogen	Gene mutation test	Reverse mutation tests with <i>Salmonella typhimurium</i> (with and without metabolic activation) Prokaryocytes	In vitro	5000; 1600; 512; 164; 52 $\mu\text{g/plate}$ 5000; 2800; 1568; 878; 492 $\mu\text{g/plate}$	
TnBP + Triton X -100 (1+5)	Gene mutation test	Reverse mutation tests with <i>Salmonella typhimurium</i> (with and without metabolic activation) Prokaryocytes	In vitro	5 μg -+ 25 μg to 5000 μg + 25000 μg	
		HGPRT test (V79 cells) (with and without metabolic activation) Eukaryocytes	In vitro	1,56+7,81 μg to 25+ 125 μg (without metabolic activation) 6,25+31,25 μg to 100+500 μg (with metabolic activation)	
	Chromosomal analysis	Rat bone marrow cytogenic test Sampling intervals: 6, 24, 48	i.v.	mg/kg /bw	
				TnBP 1,25 – 5,0	Triton X - 100 6,25-25,0
		Rats micronucleus test Sampling intervals: 16, 48, 72 hours	i.v.	mg/kg /bw	
				TnBP 1,25 – 5,0	Triton X - 100 6,25-25,0

The studies with thrombin, fibrinogen and combination of TnBP and Triton X 100 revealed no indication of gene or chromosomal damage.

- Carcinogenicity

The carcinogenicity potential of TnBP has been analysed using dietary studies conducted and reported with both the CD-1 mouse and the Sprague-Dawley rat. A treatment-related increase in the incidence of hepatocellular adenomas occurred in male mice given 585 mg/kg/day. In rats, there was a dose-related increase in the incidence and severity of hyperplasia and the incidence of papillomas of the

urinary bladder epithelium in animals given 33 mg/kg/day or above. The NOAEL for chronic toxicity was 26 and 10 mg/kg/day for mice and rats, respectively, values significantly above potential patient exposure.

Nonxynol-9 was non-toxic and non-carcinogenic in a lifetime exposure study in rats dosed intravaginally. At the potential patient exposure there is no indication of a carcinogenic risk.

- **Reproduction Toxicity**

Two studies were performed on combinations of TnBP and Triton X-100 in rats and rabbits. Pregnant animals in both studies received daily intravenously a combination of TnBP + Triton X-100 (1+5) during the period of organogenesis. The LTD's for either dams or foetuses in these conducted studies was more than 100 times greater than the dose of TnBP or Triton X-100 patients might receive when Evicel is administered.

TnBP teratogenicity studies with doses of 0, 62.5, 125, 250, 500 mg/kg/day were administered orally to pregnant Wistar rats demonstrating no significant differences in dead or reabsorbed foetuses, body weight of living foetuses or malformations. TnBP was considered to be non-teratogenic.

- **Toxicokinetic data**

Toxicokinetics studies were not submitted.

- **Local tolerance**

The local tolerance, systemic toxicity, and haemostatic properties of Evicel in comparison with Quixil were evaluated in one study of a single application in a standardized rabbit partial hepatectomy model. Macroscopic and microscopic examination of the rated site, target organs and haematological analyses were performed. No relevant clinical signs or effects were found. Only on-site adhesions were observed. There was no evidence of local intolerance, systemic toxicity and no evidence of immunotoxicity.

- **Other toxicity studies**

Immunotoxicity

Safety differences between Evicel and Quixil were assessed using a rabbit wound model. The number of cells present in the blood did not differ between both groups of animals. Results of the histopathological evaluation grading of the immunological reaction at the site of the incision did not show significant difference in any of the parameters, between the test groups and the control group.

Neurotoxicity

The effects on local tolerance and the neurotoxicity of two batches of Evicel were evaluated following subdural administration of 0.5ml fibrin sealant in the rabbit, with sham operated animals serving as controls. 10 animals were assigned to each of the three testing groups. Neurobehavioral reactions and clinical signs were monitored in a 14 days follow up period. At sacrifice, macroscopic and microscopic examination of surgical sites was performed and samples of cerebro-spinal fluid (CSF) were collected for analysis. The results of this study revealed no significant difference in all parameters tested between both batches of Evicel. Clinical signs and neurological behaviour was comparable to sham operated control group. Differences in CSF inflammation markers in both treatment compared to control group were found. 2 animals in each treatment group displayed discrete inflammation signs, none in the control animals. Macroscopic observations at sacrifice revealed that in all treatment groups fibrin sealant appeared as a thick translucent layer filling the defects and was easily detached in most cases. The sham operated defects generally appeared to be filled by tissue.

Ecotoxicity/environmental risk assessment

No studies were submitted.

Discussion on the non-clinical aspects

The non-clinical study program for Evicel is considered to be appropriate. It focuses on the evaluation of its primary pharmacological effects especially haemostatic efficacy, the frequency of occurrence of post-surgical adhesions and the stability of the clot once formed. Given the nature of the product and in view of the epislesional route of administration, additional pharmacology and pharmacokinetic studies were not deemed necessary. Results of these studies revealed no significant difference in the pharmacological performance of Evicel in comparison to other fibrin sealants. In addition, the risk of excess fibrinogen resulting from the Evicel is expected to be extremely low because of the epislesional use of the product.

Fibrin sealants/haemostatics are metabolised in the same way as endogenous fibrin, by fibrinolysis and phagocytosis.

The toxicity profile of fibrinogen, thrombin and the final formulation was not studied extensively in animals due to the fact that the components of the product are of human origin and stimulation of the immune system when introducing heterologous proteins into animals would be expected. Such an immune activation may confound interpretation of results of toxicology studies, therefore single and repeated dose toxicity, carcinogenicity and reproduction and developmental studies were neither undertaken with Evicel, nor separately with any the fibrinogen or thrombin component. However, effects of Evicel on local tolerance and neurotoxicity have been investigated by using a rabbit model and the findings do not provide evidence for a toxicological potential. Importantly, studies conducted in rabbits to evaluate the absorption and elimination of thrombin alone when applied to the cut surface of the liver resulting from partial hepatectomy revealed no evidence of enhanced thrombogenic risk for Evicel.

ADME and toxicology studies have also been conducted on the main impurities coming from the solvent-detergent based viral inactivation step of Evicel (TnBP and Triton X-100) and raised no concerns.

2.4 Clinical aspects

Introduction

Evicel was investigated in two randomized, controlled pivotal studies (see Table 5). In study 400-05-001 Evicel was used in vascular surgery and compared to the standard surgical treatment manual compression. Retroperitoneal and intra-abdominal surgery was performed in study 400-05-006, where Evicel was compared to the active comparator Surgicel. In addition eight supportive studies were conducted with Quixil.

Table 5: Pivotal Clinical Studies Conducted with Evicel

Study ID	No. study centres/ locations/ Start year	Design Control	Surgical procedure	Study Posology	Subjects Total By arm Evi/contr	Male/Female Black/White/ Other Age Range (Mean)
400-05-001	18 UK, US 2005	Phase III, single blind, standard treatment controlled, randomised Control- Manual compression	Vascular	Evicel 1-4 mL	147 75/72	77/70 26/115/6 38-90 (66.0)
400-05-006	15 US 2006	Phase III, single blind, controlled, randomised Active control - Surgicel	Urological, gynaecol., general	Evicel 0.5-10 mL Surgicel 1-300 cm ²	135 66/69	57/78 18/100/17 0-84 (55.1)

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

No pharmacokinetic studies have been conducted in man.

Pharmacodynamics

No pharmacodynamic studies have been conducted in man.

Discussion on pharmacology

Since Evicel is intended for episodic use only and intravascular administration is contraindicated, no pharmacokinetic studies have been performed in man. In addition, the product's action is based upon the well known physiological process of the final steps of the coagulation cascade and no specific pharmacodynamic studies were deemed needed.

Clinical efficacy

Two pivotal Phase III studies have been performed with Evicel for demonstration of efficacy and safety in vascular surgery (study 400-05-001) and in soft tissue bleeding in retroperitoneal and intra-abdominal surgery (study 400-05-006).

- Dose response studies

Evicel is applied by dripping or spraying directly onto the site at which haemostasis is required. Equal quantities of the two components (human fibrinogen and human thrombin) combine during application to form a thin haemostatic layer that adheres to the tissue. The dosage of Evicel is thus dependent on the area of tissue to be treated. Dosages of 0.5 to 10 mL of combined product were used in clinical trials with Evicel.

- Main studies

Study 400-05-001

This is a prospective, randomised controlled phase III study in patients undergoing vascular surgical procedures on an end-to-side femoral or upper extremity arterial anastomosis utilizing uncoated or heparin-coated polytetrafluoroethylene (PTFE) grafts. Control patients were treated with manual compression (MC).

METHODS

Study Participants

Study participants either presented with peripheral vascular disease undergoing vascular grafting or required surgery for vascular access for renal dialysis. Patients were randomised within their artery type, i.e. femoral or upper extremity. A total of 147 patients were randomised, 75 to Evicel and 72 to manual compression. Eligible were male and female patients, 18 years or older, requiring elective, primary or repeat vascular procedures with at least one end-to-side femoral or upper extremity vascular access arterial anastomosis (e.g. 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. Patients could be randomised, when following initial arterial clamp release the surgeon determined that adjunctive measures were needed to obtain haemostasis at the study anastomotic site (SAS). Patients had to provide written, informed consent before surgery.

Treatments

All patients received heparin before arterial clamping. The dosage was approximately 70 IU/kg for femoral procedures and 35 IU/kg for upper extremity artery procedures. After the surgeon had determined that adjunctive haemostatic measures were required, the randomisation envelope was broken and the patient randomised to receive either Evicel or MC. One kit of Evicel (2 ml each of the fibrinogen and of the thrombin component, total of 4 ml) was pre-prepared for each patient prior to randomisation. For patients randomised to Evicel, the required amount of product was administered by dripping onto the study anastomotic site. Arterial clamps remained in place during a further minute in order to allow time for the fibrin sealant to 'set'. In patients randomised to manual compression, arterial clamps were immediately released after randomisation and light manual pressure with sponges at the SAS was applied.

Objectives

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

Outcomes/endpoints

Primary endpoint:

- Absence of bleeding at the SAS at 4 minutes following randomisation to treatment

Secondary endpoints:

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

Sample size

The study was planned to show the superiority of Evicel over MC in stop of bleeding at 4 minutes. Based on the assumption that the proportion of patients in the Evicel group in whom bleeding was stopped at 4 minutes would be 0.63 vs. 0.35 in the MC group and a type I error of 0.05 (2-sided) it was calculated that a Chisquare test with 72 patients per group would have about 90% power to detect this difference. To account for possible drop-outs 150 patients (75 per arm) should be included into the trial.

Randomisation

Treatment was assigned randomly to each subject on a 1:1 basis. Randomisation was stratified within each participating site and also stratified for femoral versus upper extremity procedures. Ethicon provided computer-generated randomisation schedules of treatment group assignment which were placed in sealed envelopes. Each site was provided with a series of randomisation envelopes, each bearing the subject randomisation number and artery type (femoral or upper extremity) on the outside. The randomisation envelope was opened to determine the treatment allocation and at the same time the stop-clock was started and the actual time and randomisation number recorded.

Blinding (masking)

For practical reason (different form of application of Evicel and comparator) blinding was not feasible.

Statistical methods

A logistic regression model (with treatment, centre and artery type in the model) was used to assess whether there was any difference in the frequencies of responder between both treatments. Treatment effects were described by point estimates and their 95% confidence intervals. Two-sided p-values were reported for statistical tests.

For the primary endpoint, absence of bleeding at SAS 4 minutes following randomization, a significant treatment p-value (<0.05) would allow the acceptance of the alternative hypothesis, indicating a statistically significant treatment difference.

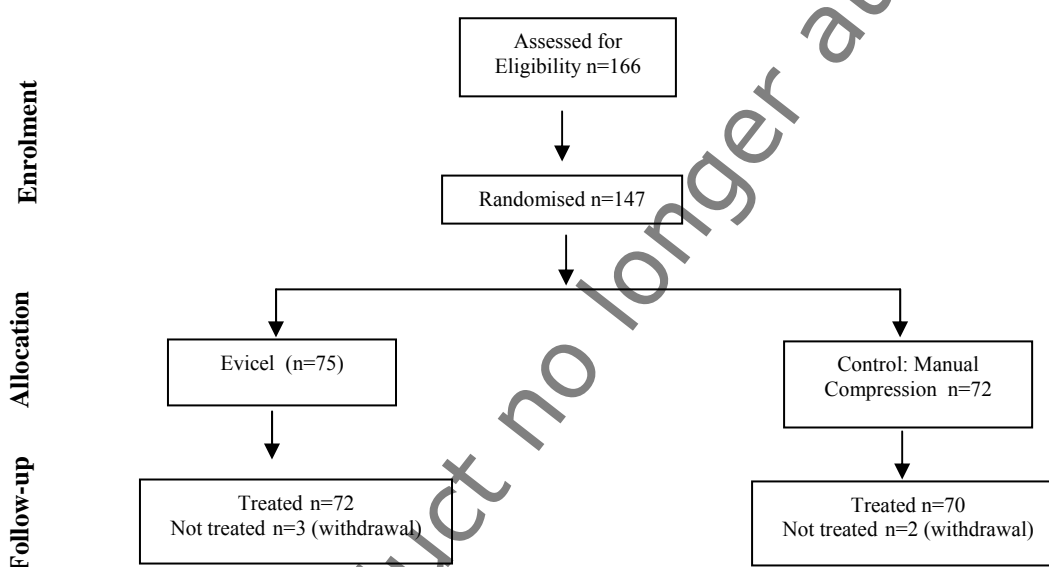
Two effectiveness analysis sets were defined in the protocol:

- Full Analysis Set (FAS) comprising all randomised patients (equivalent to the intent-to-treat (ITT) set).
- Per Protocol (PP) Analysis Set comprising all patients in the FAS who had no protocol violations.

Analysis using the FAS was considered primary. Analysis using the PP set was carried out for the primary variable only and was confirmatory.

RESULTS

Participant flow



Recruitment

The study was carried out at 5 centres in the UK and 13 centres in the US. The study population comprised patients undergoing vascular procedures utilising uncoated or heparin-coated PTFE prosthetic graft material, with at least one end-to-side anastomosis to a femoral or upper extremity artery. All patients except one (heparin-coated) had an uncoated PTFE graft. Eligible patients who had given written consent to participate in the study were randomised when suturing at the SAS was complete and the surgeon considered the suture line to be secure. If, after securing the suture line, there remained a presence of bleeding which the surgeon determined required adjunctive haemostatic measures, the arterial clamps were reapplied and the patient was considered eligible for randomisation. Following randomisation and consecutive application of Evicel or manual compression, patients were observed over a 10-minute period to determine when haemostasis was attained at the SAS. Patients were subsequently followed-up at approximately five weeks following the vascular procedure.

Conduct of the study

The majority of the 75 patients randomised to Evicel received all of the 4 ml of study treatment supplied. Seventeen (17) patients received less than 4 ml; the amount remaining unused ranged from 0.2 to 3.0 ml. The mean number of days to discharge was 5.1 (SD 8.1) in the Evicel group and 5.5 (SD 6.2) in the MC group. Two patients were not discharged from hospital following the procedure.

Baseline data

The majority (63.3%) of patients were aged between 50 and 74 years. Overall 115 (78.2%) were of Caucasian race and 26 (17.7%) were Black of African descent; none was reported to be of mixed race and five (3.5%) were Hispanic/Latino. Approximately half of the patients were ex-smokers (50.3%). Following randomisation, the treatment groups were similar in demographic characteristics.

In the Evicel group polypropylene sutures were used in all patients and these were mainly size 6-0 (55 [73.3%] patients). All patients except one (heparin coated PTFE) had an uncoated PTFE graft. In the MC group polypropylene sutures were used in all patients and these were mainly size 6-0 (47 [65.3%] patients). All patients in this group had an uncoated PTFE graft.

Numbers analysed

147 patients were randomised. Two efficacy analyses sets were defined in the protocol:

- Full Analysis Set (FAS): n=75 for Evicel and n=72 for MC.
- Per Protocol (PP): n=73 for Evicel and n=69 for MC.

Outcomes and estimation

The primary efficacy variable was the absence of bleeding at the SAS at 4 minutes following randomisation. Results for upper extremity and femoral procedures were similar (see Table 6).

Table 6: Haemostasis at 4 minutes (Full Analysis Set)

Variable	Evicel (n=75)	MC (n=72)	OR ¹	95% CI	P ²
Haemostasis at 4 minutes:					
Overall ³	64 (85.3%)	28 (38.9%)	11.3	4.7, 27.5	<0.001
Upper extremity	23/27 (85.2%)	9/21 (42.9%)			
Femoral	41/48 (85.4%)	19/51 (37.3%)			

¹ Odds Ratio. Figures greater than 1 indicate an advantage for Evicel.

² Probability.

³ The validity of the model fit is questionable due to imbalance between centre and artery type.

A highly statistically significant difference in favour of Evicel was also seen for the secondary effectiveness variables of absence of bleeding at the SAS 7 minutes and 10 minutes following randomisation (see Table 7).

Table 7: Secondary efficacy endpoints (Full Analysis Set)

Variable	Evicel (n=75)	MC (n=72)	OR ¹	95% CI	P ²
Haemostasis ≤ 7 minutes	68 (90.7%)	43 (59.7%)	7.9 ³ 6.5 ⁴	2.8, 21.9 2.6, 16.1	<0.001 <0.001
Haemostasis ≤ 10 minutes	72 (96.0%)	50 (69.4%)	18.5 ³ 10.9 ⁴	3.7, 91.8 3.1, 38.8	<0.001 <0.001

¹ Odds Ratio. Figures greater than 1 indicate an advantage for Evicel

² Probability

³ Original model. The validity of the model fit is questionable.

⁴ Revised model

⁵ Four patients were bleeding at 10 minutes and required additional haemostatic measures during 10-min observation period.

Twelve (16.0%) patients in the Evicel group and 15 (20.8%) patients in the MC group were reported to have potential bleeding related complications. There was no statistically significant difference between the groups (p=0.426). However more cases of anaemia were seen in the MC group than in the Evicel group (9 versus 5 cases).

Overall, treatment failure (defined as the presence of bleeding at the SAS 10 minutes following randomisation or the need to administer additional haemostatic measures during the 10-minute observation period), occurred more frequently in the MC group (23 [31.9%] versus 6 [8.0%] patients in the Evicel group) and this was highly statistically significant (OR 0.14; 95% CI 0.05, 0.45; $p=0.001$). Treatment failure was mainly due to the continuation of bleeding at 10 minutes (3 [4.0%] Evicel patients versus 22 [30.6%] MC patients).

Study 400-05-006

This is a phase III, prospective, randomised controlled evaluation of Evicel as an adjunct to haemostasis for soft tissue bleeding during retroperitoneal or intra-abdominal surgery.

Efficacy was evaluated by the assessment of whether Evicel was non-inferior to Surgicel, an absorbable haemostatic agent made from oxidised regenerated cellulose, in achieving haemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery.

METHODS

Study Participants

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

Procedures included, but were not restricted to the following:

- Urology: Simple or radical nephrectomy, adrenalectomy (open), radical prostatectomy and pyeloplasty.
- Gynaecology: Radical hysterectomy, radical cystectomy (bladder removal), lymphadenectomy (lymph node dissection) and primary tumour reduction surgery (*i.e.* ovarian cancer surgery).
- General surgery: Colectomy with or without anal anastomoses, low anterior resections, abdominoperineal resections and retroperitoneal tumour resection surgery.

The presence of an appropriate soft tissue TBS had to be identified intra-operatively by the surgeon. Patients had to be willing to participate in the study and must have provided written informed consent.

Treatments

Evicel or control treatment was applied to the TBS immediately after opening the randomisation envelope. Re-application was allowed at the surgeon's discretion within the 10-minute observation period. Evicel could be administered either by dripping or spraying onto the TBS.

The control group was treated with Surgicel, an absorbable haemostatic agent made from oxidised regenerated cellulose, indicated for use as an adjunct to haemostasis in surgery and used for several decades in the US. Commercially available Surgicel was provided for the clinical trial and was used within label. Both treatments were pre-prepared in total quantities of Evicel (2 x 5 mL) or Surgicel (4x8 inches [10.2 x 20.3 cm] per pack) and ready for administration for each patient.

Objectives

The study objectives were to evaluate whether the fibrin sealant Evicel was non-inferior to Surgicel in achieving haemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery.

Outcomes/endpoints

Primary endpoint:

- Absence of bleeding at the Target Bleeding Site (TBS) at 10 minutes following randomisation to treatment.

Secondary endpoints:

- Absence of bleeding at the soft tissue TBS at 4 and 7 minutes following randomisation.
- Absolute time to haemostasis (TTH).

- Incidence of treatment failure.
- Incidence of potential bleeding-related complications to end of follow-up (>7 to 14 days).
- Adverse events to end of follow-up (>7 to 14 days after surgery, clinical or telephone follow-up).

Sample size

Study 400-05-006 was planned to show non-inferiority of Evicel when compared to Surgicel with respect to haemostatic success at 10 minutes. Anticipating a success rate of 0.9 in both treatment groups and claiming non-inferiority if the lower limit of the 95% confidence interval for the ratio of success proportions ($p_{FS} / p_{Surgicel}$) is above 0.8 it was calculated, applying the method of Farrington & Manning, that 63 patients per treatment group were needed to achieve 90% power. In order to account for possible drop outs 130 patients (65 per group) should be included into the study.

Randomisation

Each site was provided with computer-generated randomisation envelopes each bearing the subject randomisation number and containing the treatment allocation. Treatment was assigned randomly to each subject on a 1:1 basis, and randomisation was stratified within each participating site. At sites capable of enrolling both adult and paediatric subjects, subjects were also stratified by age (≤ 16 , >16) and 2 sets of randomisation envelopes were provided to those sites.

Blinding (masking)

For practical reason (different form of application of Evicel and comparator) blinding was not feasible.

Statistical methods

The primary analysis variable was the haemostasis outcome at 10 minutes. The relative risk ($p_{Evicel}/p_{Surgicel}$) for achieving haemostatic success including its 2-sided 95% confidence interval was calculated using the method described by Koopman. In case the lower limit of this confidence interval was above 0.8, non-inferiority of Evicel when compared to Surgicel with respect to haemostatic outcome was assumed; in case the lower limit of this confidence interval was above 1, superiority could be concluded. Subgroup analyses by age were performed in addition.

For the primary analysis, missing values were considered as failure, for the secondary endpoints no substitution of missing values was planned. To assess the impact of missing values on the primary analysis sensitivity analyses were planned considering missing data as successes, and also, worst-case (with missing data for the Evicel group considered failures and missing data for the control group considered successes).

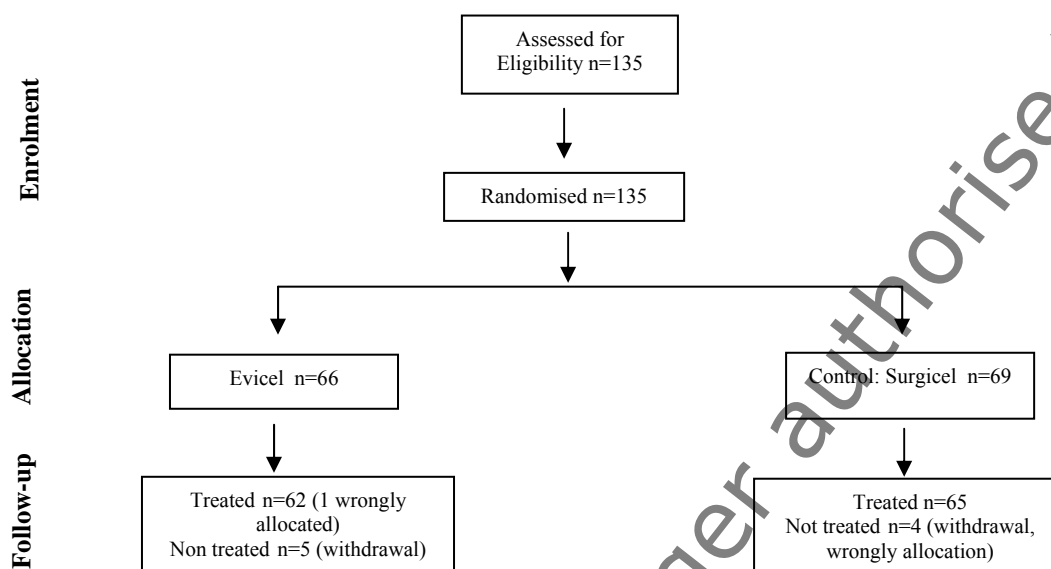
The intent to treat analysis set (ITT set) contained all subjects who were randomised. This set was split into:

- Adult analysis set (all subjects aged more than 16 years to less than 65 years)
- Paediatric analysis set (all subjects aged 16 years or less)
- Adult65+ analysis set (subjects aged 65 years or more)

The Per Protocol (PP) analysis set contained subjects in the ITT set who had no major protocol violations. The safety analysis set comprised all subjects who were randomised and received treatment.

RESULTS

Participant flow



Recruitment

The study was carried out in 17 centres located in the US.

Conduct of the study

Surgery was performed according to standard of care. The Target Bleeding Site (TBS) was identified during the retroperitoneal or soft tissue dissection as the first such site in the soft tissue presenting with mild to moderate bleeding, where conventional methods of control (i.e. suture, ligature, and cautery) were ineffective or impractical, and where an adjunct to achieve haemostasis was required.

Following identification of the TBS, the patient was randomised, the TBS was treated according to the randomisation schedule and TTH was observed. Haemostasis was defined as no detectable bleeding from the TBS at the specified time-points: 4, 7 and 10 minutes following randomisation. During the 10 minutes observation period the investigator was free to re-administer the allocated treatment. Treatment failures were defined as either the persistence of bleeding at 10 minutes following randomisation or the occurrence of breakthrough brisk bleeding that required administration of additional haemostatic measures during the 10-minute observation period. In these cases, the surgeon could apply further haemostatic measures according to his/her preference, except for the use of any fibrin sealants.

Baseline data

The median age of Evicel group was higher in comparison with the control group (57.3 vs. 53.0 years). The duration of the surgical procedures was higher in the control (Surgicel) being 213 minutes in comparison with the Evicel group 195.1 minutes. Bleeding at the TBS was mild for 61.2% of Evicel subjects and for 52.9% of Surgicel subjects. In the remainder of cases it was moderate. Cautery was used initially to achieve haemostasis at the TBS in most cases (50.7% for Evicel and 72.1% for Surgicel), with sutures and other methods (primarily clips, pressure or argon-beam coagulation) used in about 15% of cases and ligation in about 5% of cases. In 32.8% of Evicel subjects and 19.1% of Surgicel subjects none of these methods was used. The volume of the used Evicel sealant used ranged from 0.5 to 10 ml (median 5 ml). For Surgicel the quantity of product used ranged from 1 to 300 cm² (median 187.5 cm²). Reapplication was similar in both groups.

Numbers analysed

135 patients were randomised, 66 to Evicel and 69 to Surgicel. This included 11 paediatric patients aged 16 years or less (4 Evicel, 7 Surgicel). One subject was randomised to Surgicel but received Evicel in error, and is therefore in the Surgicel group when considering the ITT set (as randomised) and in the Evicel group when considering the safety set (as treated).

All patients were included in the intent to treat (ITT) analysis; 127 subjects were included in the per protocol (PP) analysis.

Outcomes and estimation

Results for the primary efficacy endpoint, absence of bleeding at the Target Bleeding Site (TBS) at 10 minutes are shown in Table 8.

Table 8: Haemostasis at 10 min

Variable	Evicel	Surgicel	RR ¹	95% CI for RR
Haemostasis at 10 min:				
ITT set	63/66 (95.5%)	56/69 (81.2%)	1.18	1.04, 1.36
PP set	59/62 (95.2%)	52/65 (80.0%)	1.19	1.05, 1.39
Adult set	32/32 (100.0%)	32/40 (80.0%)	- ²	
Adult65+ set	27/30 (90.0%)	19/22 (86.4%)	- ²	
Paediatric set	4/4 (100.0%)	5/7 (71.4%)	- ²	

¹ Relative Risk. Figures greater than 1 indicate an advantage for Evicel

² Calculation not planned

In addition, the relative proportions of success of haemostasis at 4 and 7 minutes are consistent with the 10-minute findings (see Table 9).

Table 9: Secondary Efficacy Variables (ITT set)

Variable	Evicel (n=66)	Surgicel (n=69)	RR ¹	95% CI for RR
Haemostasis ≤ 4 minutes	50 (75.8%)	37 (53.6%)	1.41	1.10, 1.86
Haemostasis ≤ 7 minutes	60 (90.9%)	53 (76.8%)	1.18	1.02, 1.40

¹ Relative Risk. Figures greater than 1 indicate an advantage for Evicel

² Potential bleeding related complications were ascertained by medical review of adverse events.

³ RR calculated for no events, due to 0 Evicel bleeding events.

⁴ p value for log rank test for comparison between treatments

Analyses indicate that in subjects in whom TBS severity was mild, 100.0% (40/40) of the Evicel treated subjects achieved haemostasis by 10 minutes compared to 89.2% (33/37) of the Surgicel treated subjects. For the subjects with moderate bleeding, 88.5% (23/26) of the Evicel subjects, compared to 71.9% (23/32) of the Surgicel subjects achieved haemostasis at the TBS by 10 minutes.

Three (3) of 66 Evicel subjects and thirteen (13) of 69 Surgicel subjects experienced treatment failures. Four of these failures were due to brisk bleeding occurring at the TBS, all of which were in Surgicel treated subjects.

- Analysis performed across trials (pooled analyses and meta-analysis)

No analysis has been performed across trials.

- Clinical studies in special populations

No studies in special populations have been performed.

- Supportive studies

Results from 8 clinical studies with Quixil were submitted in order to support the clinical data for Evicel (see Table 10).

Table 10: Supportive clinical studies conducted with Quixil

Study ID	No. study centres / locations/ Start year	Design Control	Surgical procedure Start date	Study Posology	Subjects Total By arm Qu/contr	Male/Female Black/White/ Other Age Range (Mean)
Q-LIV-008-US	15 US, UK 1999	Phase III, single blind, standard treatment controlled, randomised Active control – Avitene, Gelfoam, Oxygel, Surgicel and Surgicel NuKnit, Thrombinar, Actifoam	Liver resection	Quixil up to 10 mL	121 58/63	69/52 0/104/17 19-79 (57.1)
OFI-LIV-003-B	4 Belgium France 1996	Phase II, controlled, comparative, open Active control - Tissucol	Living related donor liver graft transplantation	Quixil 1-2 mL per 100 cm ² cut surface	34 17/17	21/13 0/34/0 0-42 (17.5)
OFI-LIV-002-UK	2 UK 1996	Phase II, open, non-comparative No control	Liver surgery	Quixil 1-2 mL per 100 cm ² cut surface	21	12/9 0/20/1 2-80 (58.0)
Q-THR009-US	US, UK 1999	Phase III, single blind, standard treatment controlled, randomised Control- Cauterization with diathermy or suture ligation	Total hip replacement	Quixil Up to 10 mL	97 38/43	53/44 6/89/2 34-88 (66.3)
OFI-TKR001-IL	3 Israel 1996	Phase II, single blind, standard treatment controlled, randomised Control- Standard surgical procedures	Total knee replacement	Quixil 10-20 mL	59 29/30	13/46 0/39/20 47-83 (69.9)
OFI-TKR004-US	US 1997	Phase III, single blind, standard treatment controlled, randomised Control- Ligation & diathermy	Total knee replacement	Quixil Up to 10 mL	53 25/28	24/29 7/45/1 41-86 (69.0)
OFI-THR005-UK	1 UK 1996	Phase II, open, pilot study Historical controls	Total hip replacement	Quixil Up to 10 mL	13	5/8 0/13/0 50-83 (67.7)
Q-CVS015-UK	1 UK 2001	Phase II, single blind, controlled, randomised Active control- Kaltostat dressing	Carotid endarterectomy	Quixil 1-5 mL	20 10/10	14/6 0/19/1 62-89 (71.7)

Discussion on clinical efficacy

A clinical study demonstrating haemostasis and suture support was conducted in a total of 147 patients (75 with Evicel, 72 with control) undergoing vascular surgery with PTFE grafts and another study demonstrating haemostasis in soft tissue bleedings in a total of 135 patients (66 with Evicel, 69 with control) undergoing retroperitoneal or intra-abdominal surgery. Efficacy has been demonstrated in both surgical settings showing superiority over comparator.

The applicant additionally sought marketing authorisation for the indication “promotion of tissue sealing”. Since no clinical studies have been performed to justify this claim, this indication could not be granted and the applicant has withdrawn this indication.

Due to the mechanism of action of a fibrin sealant, the dose solely depends on the size of the tissue to be treated and therefore dose-response studies are not applicable.

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

Clinical safety

Two Phase III clinical studies have been performed with Evicel, one in vascular surgery, the other in retroperitoneal or intra-abdominal surgery. In both studies, safety and efficacy of Evicel were compared to a control group: manual compression in vascular surgery and Surgicel in retroperitoneal or intra-abdominal surgery.

- **Patient exposure**

A total of 282 subjects were included in the two clinical trials with Evicel, 141 of which were treated with a single dose of Evicel (between 0.5 and 10 mL of combined product) and 141 of which were included in the control groups.

- **Study 400-05-001**

Adverse events

The AEs reported are summarised in Tables 11 and 12:

Table 11: Number of patients experiencing any AE

Variable	Evicel (n=75)	MC (n=72)	Total (n=147)
Total number of AEs	113	158	271
Number of patients with at least one in the following categories:			
AE	48 (64.0%)	51 (70.8%)	99 (67.3%)
SAE	23 (30.7%)	21 (29.2%)	44 (29.9%)
Severe AE	13 (17.3%)	16 (22.2%)	29 (19.7%)
AE requiring medical/surgical action	42 (56.0%)	45 (62.5%)	87 (59.2%)
Related or possibly related AE	9 (12.0%)	0 (0.0%)	9 (6.1%)

Note: Safety analysis set
Excludes pre-treatment events

Table 12: Adverse events by MEDRA coded term where an event is experienced by $\geq 5\%$ patients on any treatment.

System Organ Class	Preferred Term	Number (%)		
		Evicel (n=75)	MC (n=72)	Total (n=147)
Blood & Lymphatic System Disorders	Anaemia	0 (0.0)	5 (6.9)	5 (3.4)
Cardiac Disorders	Cardiac Failure Congestive	0 (0.0)	5 (6.9)	5 (3.4)
Gastrointestinal Disorders	Nausea	2 (2.0)	6 (8.3)	8 (5.4)
Gastrointestinal Disorders	Constipation	2 (2.7)	5 (6.9)	7 (4.8)
General Disorders & Administration Site Conditions	Oedema Peripheral	5 (6.7)	2 (2.8)	7 (4.8)
Infections & Infestations	Urinary Tract Infection	1 (1.3)	4 (5.6)	5 (3.4)
Infections & Infestations	Graft Infection	4 (5.3)	5 (6.9)	9 (6.1)
Injury, Poisoning & Procedural Complications	Vascular Graft Occlusion ¹	2 (2.7)	5 (6.9)	7 (4.8)
Injury, Poisoning & Procedural Complications	Graft Thrombosis ¹	5 (6.7)	0 (0.0)	5 (3.4)
Vascular Disorders	Hypotension	1 (1.3)	5 (6.9)	6 (4.1)

Safety Analysis Set

¹ In addition 4 patients (3 MC, 1 Evicel) had graft occlusion/thrombosis coded to the following MedDRA preferred terms: Peripheral Vascular Disease (Evicel), AV Fistula Thrombosis, Graft Infection, and Graft Complication

No treatment differences were found when assessing measurements of vital signs (systolic and diastolic BP and heart rate), requirements for blood products post-operatively or wound assessments. The safety parameters assessed in this study were coagulation parameters, full blood count and adverse events. None of the clinically significant laboratory abnormalities reported was considered to have a causal relationship to the study medication.

The adverse event profile was very much as expected in this patient population and only 9 (12.0%) patients in the Evicel group experienced adverse events that were considered to have a possible causal relationship to treatment. As the investigators considered MC to be a standard surgical technique to achieve haemostasis, rather than an investigational product, no adverse events were ascribed a causal relationship to MC.

Serious adverse event/deaths/other significant events

A total of 31 SAEs were reported in 23 patients treated with Evicel and 29 SAEs in 21 patients in the MC group. This includes four events with an outcome of death, two in the Evicel group and two in the control group.

The most frequent SAEs, in increasing order of frequency ranging from 2 to 4 patients reporting an occurrence, were graft thrombosis, incision site haemorrhage, respiratory failure and graft infection in the Evicel patients and vascular graft occlusion, respiratory failure, hypotension, peripheral ischaemia, congestive cardiac failure and graft infection in the control patients.

Seven SAEs in the Evicel patients were considered as possibly related to study treatment, whereas none of the SAEs in the control group. The control treatment of manual compression was considered by the investigators to be a standard surgical technique and not to have a potential causal relationship to the adverse events.

Cardiovascular events

Some preferred terms have been used interchangeably by the investigators, but should be taken together in order to come to a comparison between the two treatments groups. Table 13 summarizes different terms of 'complications', 'haemorrhage' and 'thrombosis/occlusion'.

Table 13: Interchangeably used terms of AE.

Term	Preferred term	Evicel (n=75)	MC (n=72)
Complication	Arteriovenous fistula site complication	1	0
	Graft complication	0	1
	Vascular graft complication	2	2
	Total	3 (4.0%)	3 (4.2%)
Haemorrhage	Anastomotic haemorrhage	0	1
	Arteriovenous fistula haemorrhage	1	0
	Graft haemorrhage	0	1
	Total	1 (1.3%)	2 (2.8%)
Thrombosis/ Occlusion	Arteriovenous fistula thrombosis	0	1
	Graft thrombosis	5	0
	Vascular graft occlusion	2	5
	Total	7 (9.3%)	6 (8.3%)
All		11 (14.7%)	11 (15.3%)

As reported 6 out of 75 (8 %) patients in the Evicel group were found to have graft thrombosis/occlusion within the first 12 days after surgery, compared to only one patient out of 72 (1.4 %) in the MC group. Later, at 5-weeks follow-up, 2 patients in the Evicel group and 5 patients in the MC group were further diagnosed with graft thrombosis/occlusion. For resolution of this complication, 7 patients (9.3%) in the Evicel group and 3 patients (4.2%) in the MC group required a surgical intervention.

The applicant provided a thorough evaluation of all cases of early graft thrombosis/occlusion adverse events (TOAE). More information on the clinical courses of the events, on the diagnostic procedures and on the surgical interventions performed was provided. After this review, four early TOAE have to be taken into consideration for the Evicel group and two patients with early TOAE in the control group.

- **Study 400-05-006**

Adverse events

The AEs reported are summarised in Tables 14 and 15:

Table 14: Number of patients experiencing any AE

Variable	Evicel (n=67)	Control (n=68)
Total number of AEs	183	200
Number of patients with at least one in the following categories:		
AE	46 (68.7%)	48 (70.6%)
SAE	12 (17.9%)	15 (22.1%)
Severe AE	6 (9.0%)	10 (14.7%)
AE requiring medical/surgical action	42 (62.7%)	46 (67.6%)
Related or possibly related AE/SAE†	1 (1.5%)	2 (2.9%)

Note: Safety set

† Causality assessment by sponsor; investigators did not consider any AEs to have a potential causal relationship to study treatment.

Table 15: Adverse events by MEDRA coded term where an event is experienced by $\geq 5\%$ patients on any treatment.

System Organ Class	Preferred Term	Number (%)		
		Evicel (n=67)	Surgicel (n=68)	Total (n=135)
Blood & Lymphatic System Disorders	Anaemia	3 (4.5)	4 (5.9)	7 (5.2)
Gastrointestinal Disorders	Nausea	9 (13.4)	6 (8.8)	15 (11.1)
	Vomiting	4 (5.0)	1 (1.5)	5 (3.7)
General Disorders & Administration Site Conditions	Oedema peripheral	6 (9.0)	4 (5.9)	10 (7.4)
	Pyrexia	7 (10.4)	6 (8.8)	13 (9.6)
Investigations	Haematocrit decreased	3 (4.5)	4 (5.9)	7 (5.2)
	Haemoglobin decreased	4 (6.0)	4 (5.9)	8 (5.9)
	Urine output decreased	3 (4.5)	5 (7.4)	8 (5.9)
Metabolism and Nutrition Disorders	Hyperglycaemia	2 (3.0)	5 (7.4)	7 (5.2)
	Hypokalaemia	8 (11.9)	7 (10.3)	15 (11.1)
	Hypomagnesaemia	3 (4.5)	4 (5.9)	7 (5.2)
Psychiatric Disorders	Anxiety	2 (3.0)	4 (5.9)	6 (4.4)
	Insomnia	8 (11.9)	6 (8.8)	14 (10.4)
Skin And Subcutaneous Tissue Disorders	Pruritis	5 (7.5)	5 (7.4)	10 (7.4)
Vascular Disorders	Hypertension	2 (3.0)	5 (7.4)	7 (5.2)
	Hypotension	5 (7.5)	9 (13.2)	14 (10.4)

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.

The safety parameters assessed in this study were coagulation parameters, full blood count and adverse events. No clinically relevant changes in clinical laboratory results were noted from the pre-operative to post-operative intervals in either of the study groups and there were no apparent differences between groups.

Serious adverse event/deaths/other significant events

A total of 34 SAEs were reported during study 400-05-006; 16 SAEs were reported in 12 patients in the Evicel group (including one event with an outcome of death) and 18 SAEs were reported in 15 patients in the Surgicel group. All were considered by the investigator to have no relationship to the study treatment. Three events were ascribed a possible relationship to the study treatment by the sponsor following medical review, one of which occurred in the Evicel group (abdominal abscess) and 2 in the Surgicel group (abdominal abscess and pelvic abscess).

The most common SAEs were urinary retention (1 Evicel, 1 Surgicel), abdominal abscess (1 Evicel, 1 Surgicel) and ileus paralytic (1 Evicel, 1 Surgicel). All other events were reported on a single occasion only. The System Organ Class which included the largest number of SAEs was Infections and Infestations with 8 events (3 Evicel, 5 Surgicel).

One death occurred during the study. Subject 22008 (Evicel) died due to hepatorenal syndrome. This event was not related to study treatment.

An internal review of adverse events that could have been potential bleeding related complications revealed that 18 patients were affected, with 7/66 (10.6%) in the Evicel group and 11/69 (15.9%) in the Surgicel group.

- Laboratory findings

Abnormalities in haematology, coagulation and biochemical parameters (anaemia, low Hb values, low haematocrit, thrombocytopenia, increased PTT, electrolyte imbalances, hyperglycemia) were reported as adverse events. The events were not considered to be related to study treatment and all patients recovered.

- Safety in special populations

The applicant provided data on group differences in adverse event frequencies for men and women. Adverse events were listed, which showed a difference in frequency of at least 5% between the Evicel group and the control group in men and in women.

Study 400-05-006 included a paediatric sub-group of 11 patients aged ≤ 16 years, of which 4 were treated with Evicel and 7 with the control product, Surgicel. The majority of adverse events were observed in the Surgicel group (27 events affecting 6 out of 7 Surgicel patients [86%]) compared to the Evicel group which reported 2 events affecting 1 out of 4 patients [25%].

- Safety related to drug-drug interactions and other interactions

Studies were not performed.

- Discontinuation due to adverse events

None reported.

- Post marketing experience

Safety data from post-marketing experience with Evicel in the US market was provided. This data incorporates the exposure and the reported adverse events since product launch (September 2006) and up to March 2008.

For a total of 81,448 kits supplied, three serious adverse drug reactions were reported for Evicel: two cases of fluid retention and one cerebrovascular accident. The latter was reported as hemiparesis during a carotid endarterectomy where Evicel was used as spray. 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.

It has to be noted, that the spray tip was held very close to the bleeding surface (about 5 cm instead of the recommended 10-15 cm, see SPC) during spraying. A contribution of Evicel to this ADR either by a thrombogenic effect or by a falsely used spray device cannot be excluded. The applicant will have to instruct the surgeons on the correct use and to report such events according to the RMP.

Discussion on clinical safety

Rarely antibodies occur after use of fibrin sealant products containing only human proteins. Due to the limited patient exposure to Evicel a possible risk for immunogenicity and for allergic reaction cannot be assessed. Data gained with the use of Quixil are of only limited value since the composition of the

products is different. This issue will be subject of post-approval surveillance and the applicant has committed to perform follow-up on immunogenicity events as a follow-up measure.

No data have been provided to substantiate the recommendation regarding the optimal temperature range for the use of Evicel. Therefore, the applicant has committed to provide in vitro data covering physical examinations to demonstrate evidence for the optimal temperature range. Temperature is supposed to have relevant impact especially on the viscosity of the components, mainly the fibrinogen component. A low viscosity is regarded a pre-condition for successful mixing of both components, and, therefore, the correct formation and quality of a fibrin clot. The applicant will perform measurements of viscosity of the fibrinogen and of the thrombin component (three lots each) in relation to temperature. (e.g. at 20°C, 25°C, 30°C, 33°C, 35°C, 37°C) as a follow-up measure.

Complications related to graft occlusion and/or graft infection and/or thromboembolic events could potentially occur in vascular surgery, due to the nature of the product and warnings have been included in sections 4.4 and 4.8 of the SPC. Since so far the number of patients treated in the critical indication of vascular surgery is quite small, the applicant has committed to gain further safety data in the context of a post-authorisation safety surveillance (PASS). This should be an observational, non-interventional study in vascular surgery, e.g. in 300 patients with submission of safety data every 100 patients or half-yearly, whatever is sooner.

The safety of fibrin sealants/haemostatics for use in human pregnancy or during breast-feeding has not been established in controlled clinical trials. Therefore, the product should be administered to pregnant and lactating women only if clearly needed and a warning has been included in section 4.6 of the SPC.

The product is intended for episional use only. Life threatening thromboembolic complications may occur if the product is unintentionally applied intravascularly and warnings have been included in sections 4.4 and 4.8 of the SPC. In addition, the applicant has committed to document difficulties with administration in a systematic way and to submit an evaluation of these data annually as a follow up measure. It is strongly recommended as well 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.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Immunogenicity, hypersensitivity, allergic reaction, anaphylaxis	Routine Pharmacovigilance	<ul style="list-style-type: none">Contraindication in section 4.3 of SPC stating: Hypersensitivity to the active substances or to any of the excipientsWarning in section 4.4 of SPC stating: As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised

		<p>urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, the administration should be immediately discontinued. In case of shock, standard medical treatment for shock should be implemented.</p> <ul style="list-style-type: none"> Undesirable effects in section 4.8 of SPC listing potential hypersensitivity and allergic reactions as well as the possible development of antibodies against components of fibrin sealants.
Thromboembolic events due to intravascular administration	Routine Pharmacovigilance	<ul style="list-style-type: none"> Contraindication in section 4.3 of SPC stating: Evicel must not be applied intravascularly Warning in section 4.4 of SPC stating: Do not apply intravascularly. Life threatening thromboembolic complications may occur if the product is applied intravascularly. Undesirable effects in section 4.8 of SPC listing potential reaction due to intravascular injection
Transmission of Infections	Routine Pharmacovigilance	<ul style="list-style-type: none"> Warning in section 4.4 of SPC stating: Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infections agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. <p>The measures taken are considered effective for enveloped viruses such as HIV, Hepatitis C Virus and Hepatitis B Virus and for the non-enveloped virus Hepatitis A Virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic</p>

		<p>anaemia).</p> <p>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.</p>
Complications related to graft occlusion, infection or thromboembolism, particularly in vascular surgery.	<p>Routine Pharmacovigilance</p> <p>Post Authorization Surveillance study (PASS) in vascular surgery.</p>	<ul style="list-style-type: none"> Undesirable effects in section 4.8 of SPC list vascular graft occlusion and graft infection as potential adverse events
Incorrect Product Application	Routine Pharmacovigilance	<ul style="list-style-type: none"> Warning in Section 4.4 of SPC stating: For epilepsional use only. Warning in Section 4.4 of SPC stating: Before administration of Evicel, care is to be taken that parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Information on development, manufacture and control of the drug substances and drug products of both components of Evicel, Human Fibrinogen and Human Thrombin were presented in a satisfactory manner. The quality data submitted indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic. Safety with regard to transmissible agents, such as human TSE and enveloped and non-enveloped viruses has been demonstrated in compliance with the relevant CHMP guidelines.

Non-clinical pharmacology and toxicology

Studies performed in bacteria to determine mutagenicity were negative for Thrombin alone, Biological Active Component (containing fibrinogen, citrate, glycine, tranexamic acid, and arginine hydrochloride), TnBP alone, and Triton X-100 alone at all concentrations tested. All concentrations of the combination of TnBP and Triton X-100 also tested negative in assays performed to determine mammalian cell mutagenicity, chromosomal aberrations and micronuclei induction.

After local application, absorption of thrombin into the plasma is slow and consists principally of thrombin degradation products which are eliminated.

No toxicological effects due to the solvent detergent reagents (TnBP and Triton X-100) used in the virus inactivation procedure are expected since the residual levels are less than 5 µg/ml.

Neurotoxicity studies performed with Evicel confirmed that subdural administration in the rabbit was not associated with any evidence of neurotoxicity. Neurobehavioral observations for 14±1 days showed no abnormal findings. No major macroscopic signs of local intolerance and no treatment – related macroscopic findings were observed. Analysis of cerebrospinal fluid did not reveal major signs of inflammation.

Efficacy

Efficacy has been demonstrated showing superiority in two Phase III randomised, controlled clinical studies with Evicel. One study in haemostasis and suture support was conducted in a total of 147 patients (75 with Evicel, 72 with control) undergoing vascular surgery and another study in haemostasis of soft tissue bleedings in a total of 135 patients (66 with Evicel, 69 with control) undergoing retroperitoneal or intra-abdominal surgery. In both studies, efficacy of Evicel was compared to a control group: manual compression in vascular surgery and Surgicel in retroperitoneal or intra-abdominal surgery.

In study 400-05-001 (vascular surgery) 85.3 % of patients treated with Evicel had ceased suture bleedings four minutes after randomisation, improving up to 96.0% at the end of the observation period at 10 minutes after randomisation. For comparison, manual compression was effective in 38.9% after 4 minutes and finally in 69.4% of patients. Treatment failures occurred in 8.0% (Evicel) versus 31.9% (MC) of subjects. Similar efficacy results were found in study 400-05-006 (retroperitoneal or intraabdominal surgery) on soft tissue bleedings with a success rate of 95.5% haemostasis at the target time point of 10 minutes after randomisation compared to 81.2% in the active control group. Treatment failures occurred in 4.5% (Evicel) versus 18.8% (Surgicel) of subjects.

The applicant additionally sought marketing authorisation for the indication “promotion of sealing”, however, since no clinical studies have been performed to justify this claim, this indication could not be granted and the applicant withdrew this indication.

Data are too limited to support the safety and effectiveness of Evicel in children.

Safety

A total of 282 subjects were included in two clinical trials with Evicel, 141 of which were treated with a single dose of Evicel (between 0.5 and 10 mL of combined product) and 141 of which were included in the control groups.

In the study in retroperitoneal and intra-abdominal surgery (study 400-05-006) involving 135 patients (67 patients were treated with Evicel and 68 were control group patients) no adverse events were considered to be causally related to the study treatment according to the investigator assessments. The sponsor considered three serious adverse events (SAE) (abdominal abscess [2], pelvic abscess) as being possibly related to study treatment, one of them in the Evicel group.

Adverse reactions which may be reported in rare cases in association with fibrin sealants are hypersensitivity or allergic reactions. Section 4.8 of the SPC gives general information. However, since no such reactions have been reported during clinical trials with Evicel, the frequency of these events with Evicel is not known.

In study 400-05-001 in patients undergoing vascular grafting procedures involving 147 patients (75 with Evicel, 72 with control), a total of 16 subjects were reported to have had a graft thrombosis/occlusion adverse event during the study period (5-week observation period) being the events evenly distributed across treatment arms. However, the risk was higher in the first 12 post-operative days in the Evicel group with an increased need for surgical intervention compared to the control group. Review of all cases of thrombosis/occlusion adverse events (TOAE) at this time point identified four cases of early TOAE in the Evicel group and two cases in the control group.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The applicant's request for a waiver is not granted. Therefore, the applicant committed to perform a user testing post-authorisation.

Risk-benefit assessment

The benefit/risk assessment regarding quality, non-clinical and clinical aspects of Evicel is considered to be positive in "supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis and as suture support for haemostasis in vascular surgery" when used by experienced surgeons. The manufacturing process of Evicel has been optimized and validated to ensure consistent quality and safety of Evicel's Human Fibrinogen as well as Human Thrombin component. The non-clinical testing program for Evicel revealed no evidence for a particular toxicological risk for the intended clinical use. The clinical development program comprised two randomized clinical trials, one in retroperitoneal and intra-abdominal surgery, and one in vascular surgery. Efficacy results of both studies indicated superiority of Evicel over the control treatment. No safety concerns derived from the study in retroperitoneal and intra-abdominal surgery. However, thrombotic events or occlusion of the graft (four cases of early TOAE in the Evicel group and two cases in the control group), became an issue of concern from the study in vascular surgery. Although these findings were not statistically significant, it has to be noted that complications related to graft occlusion and/or graft infection and/or thromboembolic events could potentially occur in this kind of surgery and due to the nature of the product. The CHMP considers that at this point the risk does not overcome the benefits of Evicel. Since so far the number of patients treated with Evicel in the critical indication of vascular surgery is quite small and in order to gain better understanding on the safety of the product, the applicant has committed to perform an observational, non-interventional post-authorisation safety surveillance (PASS) in vascular surgery as a follow-up measure.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, non-clinical pharmacology and toxicology, and clinical safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Evicel in supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis and as suture support for haemostasis in vascular surgery was favourable and therefore recommended the granting of the marketing authorisation.