EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/474697/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name Evicel

Procedure No. EMEA/H/C/000898/II/0021

Marketing authorisation holder (MAH): Omrix Biopharmaceuticals N. V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
BAC2	Biologically active component 2
BMI	Body Mass Index
CDC	Center for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran Mantel-Haenszel
CSF	Cerebrospinal fluid
CT	Computed tomography
DHPC	Direct Healthcare Professional Communication
DVT	Deep Vein Thrombosis
EC	European Commission
FAS	Full Analysis Set
GCP	Good Clinical Practice
ITT	Intent to Treat
IU	International Units
IV	Intravenous
MAH	Marketing Authorization Holder
MedDRA	Medical dictionary for regulatory acitivities
n/a	Not applicable
NHSH	National Healthcare Safety Network
OR	Odds ratio
PDCO	Paediatric Committee of the European Medicines Agency
PI	Product Information
PIP	Paediatric Investigation Plan
PP	Per Protocol Set
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
RSI	Request for supplementary information
SA	Scientific Advice
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SmPC	Summary of product characteristics
SOC	Standard of Care
SSA	Surgical site assessment
SSI	Surgical site infection
SUSAR	Suspected Unexpected Serious Adverse Drug Reactions
TA	tranexamic acid

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Omrix Biopharmaceuticals N. V. submitted to the European Medicines Agency on 3 October 2012 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Evicel	HUMAN FIBRINOGEN / HUMAN THROMBIN	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication to include use as a tissue glue to promote adhesion/sealing, or as suture support in neurosurgery and surgical procedures where contact with cerebro-spinal fluid or dura mater can occur and a modification of the wording of existing indication as "as a tissue glue to promote adhesion/sealing, or as suture support in vascular surgery. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 5.1 and 5.3 of the SmPC and the Package Leaflet was proposed to be updated accordingly. Minor modifications to the SmPC, Labelling and Package Leaflet have also been proposed.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Rapporteur: Jan Mueller-Berghaus

Co-Rapporteur: Piotr Feodor

1.2. Steps taken for the assessment

Submission date:	3 October 2012
Start of procedure:	23 November 2012
Rapporteur's preliminary assessment report circulated on:	17 January 2013
Co-Rapporteur's preliminary assessment report circulated on:	15 January 2013
Rapporteur/Co-Rapporteur's joint assessment report circulated on:	14 February 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 February 2013
MAH's responses submitted to the CHMP on:	27 March 2013
Rapporteur's preliminary assessment report on	23 May 2013

the MAH's responses circulated on:	
Request for supplementary information and extension of timetable adopted by the CHMP on:	30 May 2013
MAH's responses submitted to the CHMP on:	5 June 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	19 June 2013
CHMP opinion:	27 June 2013

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0025/2012 on a PIP and an EMA Decision on a PIP modification P/0193/2012.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on 28 September 2009. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier (EMEA/H/SA/1377/1/2009).

2. Scientific discussion

2.1. Introduction

In neurosurgery, cerebrospinal fluid (CSF) leakage is considered to be one of the most challenging and potentially dangerous complications. Among the envelopes which contain and protect the neural structures, the dura mater is the only one that can be surgically repaired. Watertight closure of the dura is the first line of protection from postoperative CSF leakage, which can lead to other serious complications such as meningitis and delayed wound healing. (1)

Fibrin sealants -generally containing two major components, fibrinogen and thrombin - manufactured from pooled human plasma have been used in surgery since the 1970s both for haemostatic purposes but also for sealing, reinforcement of sutures and tissue adhesion (2, 3).

Most fibrin sealants also contain an antifibrinolytic agent to stabilise the fibrinogen in vitro by avoiding degradation by plasminogen which may be present as an impurity in the fibrinogen concentrate, and/or to stabilise the clot in vivo. Commonly used antifibrinolytic agents are bovine aprotinin and tranexamic acid (TA) although both have disadvantages. TA has been shown to have neurotoxic potential (ref 4)) and thus fibrin sealants incorporating TA are contraindicated for use in neurosurgery and surgical procedures where contact with CSF or dura mater can occur. Bovine aprotinin on the other hand is potentially antigenic; severe allergic and anaphylactic reactions have been reported (5,6). Such reactions occur more frequently in patients who have been exposed previously to aprotinin-containing products, particularly

within the prior 12 months. The development of EVICEL was based on that of a previous product manufactured by OMRIX biopharmaceuticals and marketed in the EU/EEA as QUIXIL and in the USA as CROSSEAL. In contrast to Quixil, EVICEL does not contain the potentially neurotoxic antifibrinolytic agent tranexamic acid (TA).

EVICEL is a human plasma-derived fibrin sealant product which consists of two biological components, Human Fibrinogen and Human Thrombin, presented as separate solutions. Thrombin is formulated with calcium chloride and stabilized with Human Albumin Solution. When the two solutions are combined, conversion of fibrinogen into fibrin occurs, replicating the final step of the coagulation cascade. Calcium ions are required for the conversion of fibrinogen and the cross linkage of fibrin. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

Evicel is approved for the following indication: '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.'

The MAH (Omrix/ Ethicon) by this submission is proposing to add a new indication and modify the currently approved - as follows:

"EVICEL is used as supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis.
EVICEL is also indicated as a tissue glue to promote adhesion/sealing, or as suture support:
- In vascular surgery.
- In neurosurgery and surgical procedures where contact with cerebro-spinal fluid or dura mater can occur"

EVICEL is only indicated for use in adult subjects and no paediatric indication has been sought with the current variation application.

The claim is based on an additional study (Study No. 400-09-001) investigating the use of EVICEL in neurosurgery as an adjunct to sutured dural repair.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical information contained in this application summarised data previously submitted for the approval of Evicel and included additional primary pharmacology and toxicology data from a Canine Durotomy Model (Study No. 08-0002) study as applicable for this extension of indication. The local tolerance and neurotoxicity study in white rabbits (Study No 23597) which was assessed as part of the original application is re-discussed here as considered relevant. An additional study on a dog model of gastrointestinal anastomosis was submitted but not assessed as not relevant to the claimed indication.

2.2.2. Pharmacology

One additional pharmacology study was submitted in support of this indication; Dural Sealing Efficacy of Evicel in a Canine Durotomy Model (Study No. 08-0002).

Study No. 08-0002 was a study in a canine model of durotomy repair with the primary objective to assess the efficacy and safety of EVICEL in preventing cerebrospinal fluid (CSF) leakage when compared to

another fibrin sealantand a synthetic surgical sealant marketed in the US as a medical device for use as an adjunct to sutured dural repair during cranial surgery.

Following durotomy, the cut dural edges were approximated with 3 interrupted 6-0 polypropylene sutures, placed loosely at equal intervals, leaving a 2 mm x 20 mm gap to ensure there was the potential for CSF leakage. An infusion of methylene blue was administered in order to visualize any subsequent loss of CSF at intracranial pressures (ICP) of ≥ 15 mmHg. Sealants were applied at a target dose of 1–2 mL/site, with 2 animals receiving a lower volume (0.5 and 0.8 mL) and 1 receiving a higher volume (3 mL). Animals in Group 1 received EVICEL, animals in Group 2 received the fibrin sealant, and animals in Group 3 received the medical device. The ICP was monitored until it achieved a level of approximately 15 mmHg. The cisternal catheter was then removed, and the surgical site was closed with suture.

Physical examinations were performed before surgery. At protocol-specified time points, clinical observations and neurological examinations were performed and body weights were recorded. Before surgery and again before necropsy, blood samples were collected for hematology and serum chemistry analyses. On the day of necropsy, each animal was anesthetized to allow reopening of the craniotomy site and to allow scoring of the durotomy site for sealant adherence to the dura. Assessment of CSF leakage at the durotomy site was also performed before necropsy by raising the ICP at least 55 mmHg for inspection of CSF leakage. Histopathological analysis was performed on selected tissues.

There were no observations of CSF leakage at the durotomy site before necropsy at baseline and at raised ICP (at least 55 mmHg) in all groups, with the exception of one animal treated with the synthetic comparator product.

During the study, there was little intergroup variation in bleeding; a slight increase in EVICEL group hemorrhage observed on Day 2 away from the durotomy site was not considered significant and resolved during the follow-up period. Similarly, at Day 8, bleeding observed in the EVICEL group was in 2/9 animals, spatially restricted, and there was minimal variation at the group level. Since the sealant was applied to a CSF leak rather than a vascular site, the observation of bleeding is not thought to be related to the test article, but rather the surgical approach to the dura.

At Day 29 following surgery, microscopic tissue changes induced by EVICEL at the durotomy site were similar in nature to those induced by the comparator products. There was a less marked histiocytic response in the animals treated with EVICEL than in those treated with the synthetic comparator product, while the fibrovascular response induced by EVICEL appeared to be slightly greater than that induced by the other sealants at this interval. Due to the different absorption rates for the products, transient differences at single time points are anticipated; however the long term outcome is considered equivalent.

All animals survived until scheduled euthanasia. There were no sealant-related clinical observations, neurological effects, or clinical pathology changes attributed to the sealants tested. Changes in clinical signs and clinical pathology parameters which were observed could be attributed to postoperative stress and analgesic therapy.

The study concluded that EVICEL was similarly efficacious in preventing cerebrospinal fluid leakage when compared to comparator sealants in this model of neurosurgery.

2.2.3. Pharmacokinetics

No additional pharmacokinetic studies were submitted as part of this extension of indication.

2.2.4. Toxicology

Data on local tolerance and neurotoxicity of are presented as relevant to this indication.

Local Tolerance

The local tolerance was evaluated following a single subdural application in 3 groups of 10 female New Zealand white rabbits (study 23597 – submitted within the original application of Evicel, summarised here). 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.

Other toxicity studies

Neurotoxicity

Neurotoxicity in the Primary Pharmacodynamic Canine Durotomy Model

In the efficacy study of mongrel dog durotomy sealing clinical and behavioural assessments as well as macro- and micro-histologic evaluation of the tissues were included. This study concluded that when used for dural sealing, no sealant-related clinical or neurobehavioural effects were observed and the microscopic tissue changes at the surgical site were similar to those induced by comparator products. In addition, there was a less marked histiocytic response in the animals treated with EVICEL than in those treated with the synthetic comparator product, while the fibrovascular response induced by EVICEL appeared to be slightly greater than that induced by the other sealants in animals euthanized on Day 29, such proliferation reflects continued healing of the dura.

No major macroscopic signs of local intolerance and no treatment-related abnormal macroscopic findings were observed. The fibrin sealant regularly appeared as a thick translucent material filling the defects and was easily detached in most cases.

Neurotoxicity in rabbits (study 23597)

Neurotoxicity of EVICEL was evaluated in study 23597 using two batches of Evicel (Nabi-cryo/ZLB-cryo) following subdural administration 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.
The rabbits were anaesthetized and a total dose of 0.5 mL of EVICEL in which the Fibrinogen component was derived from different sources of cryoprecipitate intermediate (referred to in this study as BAC2/1 and BAC2/2) was applied to two standardized surgical sites, following bilateral parasagittal craniotomy and creation of defect of the dura mater at each side. Sham operated animals were used as controls but no fibrin sealant was applied. The animals were then sutured and neurobehavioral observations were made for 14±1 days. At the end of the study, the animals were killed and the surgical sites were subject

to macroscopic and microscopic examination and samples of cerebrospinal fluid were collected for analysis.

There were no abnormal clinical or neurobehavioral signs indicating an adverse effect of EVICEL. The defects in the sham operated animals generally appeared to have been filled by tissue. Analysis of the cerebrospinal fluid did not reveal major signs of inflammation or any difference between the two EVICEL groups and the sham operated control, beyond discrete inflammation observed in 2 animals in each of the EVICEL groups. The microscopic tissue response to EVICEL in which the Human Fibrinogen component was manufactured from different sources of cryoprecipitate intermediate, was similar and biologically significantly different from the tissue response within the sham operated control sites. The two test articles were surrounded by fibrous tissue infiltrated by heterophils and macrophages. Both EVICEL formulations were associated with accumulations of inflammatory cells, typical for fibrin sealant implants. The fibrous tissue response merged with the dura mater. The inflammatory component of the response to the test articles decreased as it merged with the dura mater. Adhesions between the fibrous tissue and the pia mater generally involved the entire length of the defect and were more severe in the animals given EVICEL than were observed for the control animals. The inflammatory responses, as well as the observation of adhesions between the fibrous tissue and the pia mater were both expected findings with fibrin sealants and were associated with physiological processes of product degradation in the implanted tissues. The study concluded that EVICEL did not cause any treatment related local or systemic neurotoxicity.

2.2.5. Ecotoxicity / Environmental Risk Assessment

No environmental risk assessment was submitted (see discussion)

2.2.6. Discussion on non-clinical aspects

The preclinical aspects of human fibrinogen / human thrombin were already documented in the original dossier where the preclinical pharmacology and toxicology programme has been considered adequate. Additional information relevant to the use of the product as tissue glue to promote adhesion/sealing or as suture support in neurosurgery and surgical procedures where contact with CSF or dura mater can occur is provided from a new study on dural sealing efficacy in a canine sealing model. Data from a previously submitted neurotoxicity and local tolerance study in rabbits are re-discussed in the context of the new indication.
The durotomy repair study in mongrel dogs was conducted to assess the efficacy and safety of EVICEL in preventing cerebrospinal fluid (CSF) leakage in comparison to another fibrin sealant and a synthetic surgical sealant marketed as a medical device for use as an adjunct to sutured dural repair during cranial surgery. The methodology was described by Preul et al, 2003 who confirmed that this model results in a persistent CSF leak if not treated with a sealant. Evicel and the other sealants used in this study have been applied by dripping.

The study concluded that EVICEL was similarly efficacious in preventing cerebrospinal fluid leakage if compared to the other two haemostatic products in this model of neurosurgery. However, these findings have limited significance in view of the limitations of the study. First of all only a low number of animals has been tested (i.e. 3 per group) and no untreated controls have been included, however it can be argued that sham operated animals are not necessary as there are historical controls. Furthermore, the sealing efficacy of Evicel should have been investigated in a study testing different doses of Evicel as this would have been helpful to gain some information on the “dose” to be applied to assure sealing efficacy. The provided non-clinical pharmacodynamic data although suggestive of efficacy, are not considered indeed relevant for approval of the requested variation. However, further studies using such animal

models are not considered useful since they do not reveal further relevant knowledge taken into account that clinical experience has already been obtained.

Certain aspects of animal toxicity testing were not considered applicable to the profile of human fibrinogen / human thrombin 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 the fibrinogen or thrombin components, which is acceptable.

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. These results were already included in the original dossier. Further, in the durotomy sealing study in the mongrel dog clinical and behavioural assessments as well as macro- and micro-histologic evaluation of the tissues were included. In this study it was concluded that no sealant-related clinical or neurobehavioural effects were observed and the microscopic tissue changes at the surgical site were similar to those induced by the comparator products. There were no abnormal clinical or neurobehavioral signs indicating an adverse effect of EVICEL. No major macroscopic signs of local intolerance and no treatment-related abnormal macroscopic findings were observed. As expected in the Evicel treated animals the degree of inflammatory response was increased, as well as the observation of adhesions between the fibrous tissue and the pia mater. The dose was chosen to represent a "normal" dose as applied to humans, no further doses have been tested, as EVICEL will be applied per thickness and not per dose - as such calculating an overdose in the traditional sense would not be possible.

The type and amount of animal studies on neurotoxicity and local tolerance are in principle considered sufficient to support the requested indication expansion; the results provided so far do not reveal concerns in terms of neurotoxicity and local tolerance.

The application of Evicel - as with other fibrin sealants - is associated with the induction of inflammation, fibrous tissue response and adhesions. These aspects are discussed in the context of clinical safety and considered within the overall benefit risk analysis.

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), EVICEL is exempt from the requirement for an environmental risk assessment because its constituents and metabolites are unlikely to result in significant risk to the environment.

2.2.7. Conclusion on non-clinical aspects

Non-clinical data are adequate and no further information is needed. The study on local tolerance and neurotoxicity in rabbits was already submitted at time of MAA. Thus, the results of this study are already stated in the SmPC as follows:

> *Section 5.3 Preclinical safety data*
>
> *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.*

This wording is considered adequate and appropriate to reflect the results of this study in view of the extension of the indication. No further revisions in the SmPC are warranted on preclinical aspects.

2.3. Clinical aspects

2.3.1. Introduction

A pivotal study has been submitted in support of the proposed indication for EVICEL -as a tissue glue to promote adhesion/sealing in neurosurgical procedures- evaluating the use of EVICEL as an adjunct to dural sutures in elective cranial surgery, providing intra-operative watertight closure (study 400-09-001).

The proposed extension / modification of the indication:
EVICEL is also indicated as a tissue glue to promote adhesion/sealing, or as suture support:
- In vascular surgery.
- In neurosurgery and surgical procedures where contact with cerebro-spinal fluid or dura mater can occur"

is based on the results of pivotal study (400-09-001 of INN) in the new target population of patients undergoing an elective posterior fossa or supratentorial procedure (craniectomy or craniotomy), upon completion of the primary sutured dural repair and evaluation of the closure for intra-operative cerebrospinal fluid (CSF) leakage.

GCP

The clinical trial was 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. This applies to study Protocol Number 400-09-001 which included Australia as Non-EU country.

Table 1 Tabular overview of clinical studies with Evicel

Protocol No / Title / No of centres / Location	Completion status / Start date / Subjects enrolled	Study design / Control type	Dose treatment	Study objective
400-09-001 Adjunct to sutured dural repair 14 UK, Belgium, Finland, France, Germany, Netherlands, Australia	Completed / October 2011/ 139 89/50	Phase III single – blind, controlled, randomised / sutures	Evicel up to 4 mL by dripping or spraying	To evaluate safety - efficacy of Evicel for use as an adjunct to dura sutures in elective cranial surgery to provide intra-operative watertight closure

2.3.2. Clinical Pharmacology

No clinical pharmacology data were submitted.

2.3.3. Discussion on Clinical Pharmacology

Evicel is for epilesional use only and thus pharmacokinetic investigations do not apply. No additional clinical pharmacology studies are considered necessary.

2.4. Clinical Efficacy

The application in support of the indication “as a tissue glue to promote adhesion/sealing, or as suture support in neurosurgery and surgical procedures where contact with cerebro-spinal fluid or dura mater can occur” was based on the results of study 400-09-001.

2.4.1. Dose Response studies

No dose response studies are submitted (see discussion on Clinical aspects).

2.4.2. Main Study

400-09-001

This was a randomized, controlled study to evaluate the safety and effectiveness of EVICEL as an adjunct to sutured dural repair.

Methods

Study participants

Main inclusion criteria

Subjects should be ≥ 18 years, undergoing elective craniotomy/craniectomy for pathological processes in the posterior fossa (such as benign or malignant tumors, vascular malformation, and Chiari 1 malformations) or in the supratentorial region and who were demonstrated to have persistent CSF leakage following primary attempt at suture closure of the dural incision, they should be administered antibiotic prophylaxis perioperative.

Intra-operative criteria for patients' eligibility were:

- Surgical wound classification Class I. Penetration of mastoid air cells during partial mastoidectomy was permitted.
- The cuff of native dura along the craniotomy edge on each side was wide enough based on surgeon's judgment to facilitate suturing and to allow for sufficient surface area for adherence of the investigational product.

Exclusion criteria

Preoperative subjects would be excluded from the study if:

- A dura lesion from a recent surgery that had the potential for CSF leakage
- Chemotherapy or Radiation therapy to the head was scheduled within 7 days following surgery
- Long-term (6 months) low dose steroid therapy for existing chronic/inflammatory conditions to be resumed within 7 days following surgery. However, postoperative tapered high-dose steroids were permitted.
- Severely altered renal function as confirmed by local laboratory reference ranges for serum creatinine and/or hepatic function [alanine aminotransferase (ALT), aspartate aminotransferase (AST) > 5 x upper limit of normal (ULN)]
- Evidence of an infection indicated by any one of the following: clinical diagnosis of infection, fever, positive urine culture, positive blood culture, positive chest X-ray, evidence of infection along the planned surgical path. A WBC count of <20000 was permitted if the subject is being treated with steroids in the absence of all the other infection parameters.
- Conditions or treatments significantly compromising the immune system (such as Acquired Immune Deficiency Syndrome).
- Known hypersensitivity to the components of the investigational product (human fibrinogen, arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, human thrombin, human albumin, mannitol and sodium acetate).
- Non-compliant or insufficient treatment of diabetes mellitus in the opinion of the investigator.
- Hydrocephalus, except occlusive hydrocephalus caused by posterior fossa pathology to be treated.
- Existing CSF (ventricular, etc.) drains, Cushing/Dandy cannulation or Burr holes which damage the dura.
- Female subjects of childbearing potential with a positive urine or serum pregnancy test within 24 hours prior to surgery.

- Female subjects who were breastfeeding, pregnant, or intended to become pregnant during the clinical study period.
- Participation in another clinical trial with exposure to another investigational drug or device within 30 days prior to enrollment.
- Scheduled or foreseeable surgery within the follow-up period.

In the intra-operative phase subjects would be excluded if:

- Dura injury during craniotomy/craniectomy that could not be eliminated by widening the craniotomy/craniectomy to recreate the native dura cuff
- Use of implants made of synthetic materials coming into direct contact with dura (e.g., polytetrafluoroethylene (PTFE) patches, shunts, ventricular and subdural drains)
- Planned use of dural patches after primary suture closure of the dura
- Placement of Gliadel Wafers
- Persistent signs of increased brain turgor
- Subject had a gap between durotomy edges of greater than 2mm after primary dural closure
- Intersecting durotomy scars in the surgical path from a previous operation that could not be completely removed by the planned dura resection
- Two or more separate dura defects
- Major intra-operative complications that require resuscitation or deviation from the planned surgical procedure

Treatments

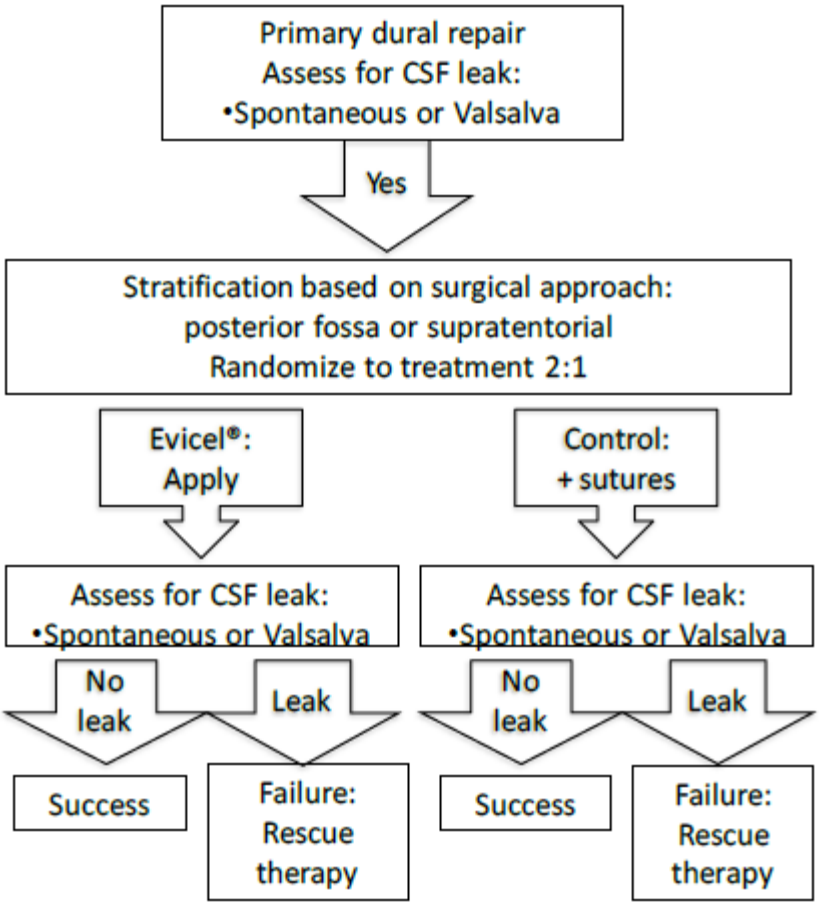
For each subject randomized to EVICEL, one kit of EVICEL (total 4 ml) was pre-prepared in the applicator kit prior to randomization. For subjects randomized to receive EVICEL, the fibrin sealant was to be applied by either dripping or spraying as a thin layer to the entire length of the suture line and the adjacent area to at least 5mm away, including all suture holes. If necessary, a second layer of EVICEL could be applied. A cure time of 1-2 minutes was to be allotted between layers to allow for polymerization.

After treatment CSF leakage was re-evaluated with the Valsalva maneuver performed to an intrathoracic pressure of 20-25 cm H2O for 5-10 seconds. If CSF leakage was still apparent a second treatment (up to two layers) with EVICEL could be applied. CSF leakage was re-evaluated with the Valsalva maneuver (see study design in figure 1).

If watertight closure was not evident after this final Valsalva maneuver, the response was to be deemed a failure and the surgeon was to revert to standard of care (SOC) for closure including the use of other commercially available fibrin sealants (except EVICEL) or an onlay dural patch. If watertight closure was achieved, no adjunct was to be used. Closure of the remaining layers of the surgical site was to be performed according to the surgeon's standard of practice.

Subjects randomized to control received additional dural sutures as deemed necessary by the surgeon. CSF leakage was evaluated with the Valsalva maneuver performed to an intrathoracic pressure of 20-25 cm H2O for 5-10 seconds.

Figure 1 Study design (Study No. 400-09-001)



Objectives

The objective of the study was to evaluate the safety and effectiveness of EVICEL for use as an adjunct to dura sutures in elective cranial surgery to provide intraoperative watertight closure.

Outcomes / endpoints

The primary efficacy endpoint was the proportion of successes (intra-operative watertight closure) in the treatment of intra-operative CSF leakage. Success was defined as no CSF leakage from dural repair intra-operatively, during Valsalva maneuver 20-25 cm H2O for 5-10 seconds.

Secondary endpoints were the following safety variables

- Incidence of CSF leakage within 5 days (± 2) post-operatively (wound healing assessment)
- Incidence of CSF leakage within 30 days (± 3) post-operatively (wound healing assessment)
- Incidence of adverse events (AE)
- Incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (± 3) post-operatively

Sample size

Due to the sequential study design no fixed sample size was calculated. The maximum sample size for a triangular design with continuous monitoring was contrasted with the sample size for a fixed design. Anticipating a success rate of 70% in the control arm, a success rate of 90% in the treatment arm, a 2-sided type I error of 0.025 and 90% power a maximum sample size of 322 subjects was calculated in case of a continuously monitored triangular test and an 2:1 (active: control) allocation . The corresponding number of subjects in a fixed sample design was calculated to be about 221 subjects.

Simulations were performed to assess power and the expected sample size under different assumptions on treatment effects

Randomisation

Subjects were randomized applying a 2:1 (active: control) ratio stratified by predetermined surgical approach (posterior fossa / supratentorial).

Each site was provided with a computer-generated set of randomization envelopes to be opened once intra-operative eligibility was confirmed. In the event that a potential subject failed intra-operative criteria, and was not randomized to the study, the unused randomization envelope was to be returned to the series, and used for the next subject.

Blinding (masking)

Blinding was not performed.

Statistical methods

The following analysis sets were to be defined:

- The Safety Analysis Set was to contain all subjects who were randomized and received treatment.
- The FAS was to contain all randomized subjects (equivalent to the Intent-to-Treat [ITT] set) that were analyzed at the interim analysis where the study was stopped by the independent statistician.
- The Per Protocol Set was to contain subjects in the FAS who have no major protocol violations (these were to be agreed at a pre-database lock meeting).
- If there were any “over-run” subjects (recruited after data that was sent to the independent statistician resulted in the study being stopped, then a further analysis set (FAS over-run) was to consist all randomized subjects.

A sequential triangular test was used to analyse the primary endpoint (proportion of subjects achieving successful watertight closure) based on the ITT population of all randomized subjects. The triangular test for a binary response variable was used (PEST 4.4 software) with a two-sided alpha 0.025 and power 0.90.

For this analysis missing endpoint information was considered as treatment failures. The first analysis was planned to include the first 135 subjects randomized with further analyses at completion of every 45 subjects if required. At each interim analysis the value of the appropriate test statistics were calculated and compared with the appropriate stopping boundary (adjusted for discrete monitoring). In case the upper boundary was crossed, the study was stopped and the superiority of Evicel over control treatment was concluded.
As part of sensitivity analyses the primary analysis was repeated considering missing data as successes, as worst-case analysis (missing Evicel data as failure, missing control group data as successes) and as best-case analysis (missing Evicel data as success, missing control group data as failure).

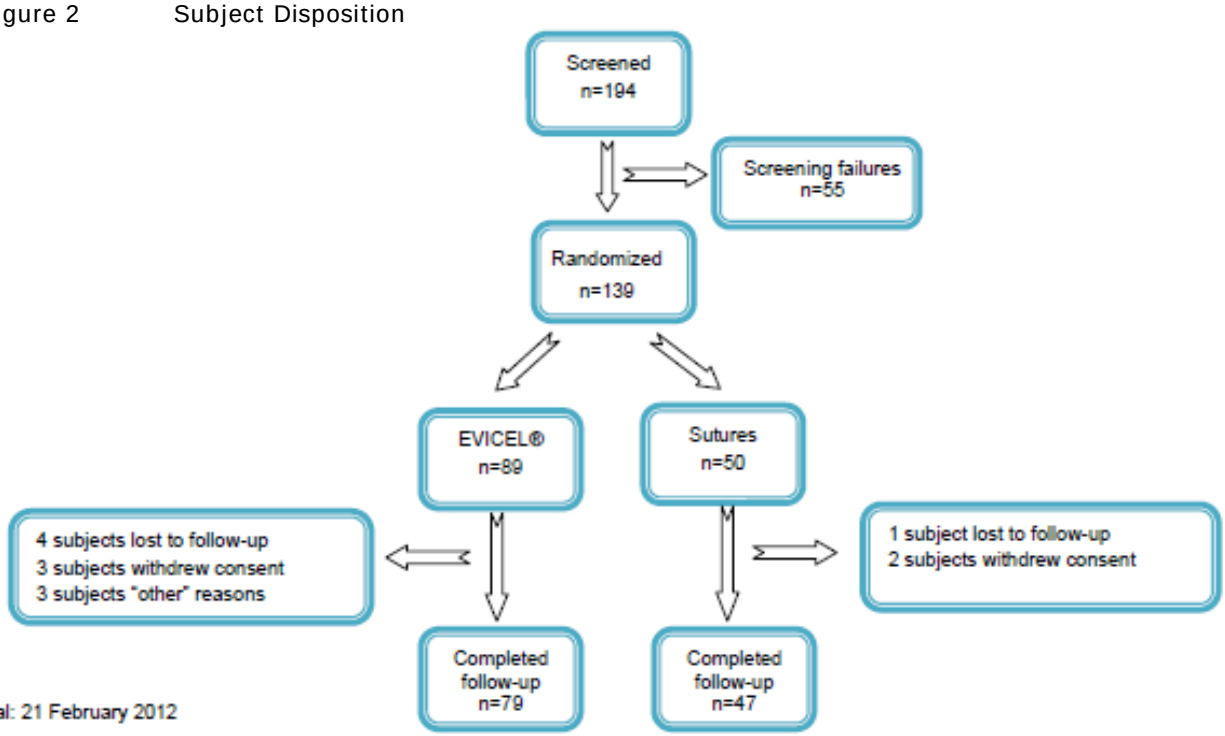
Logistic regression with treatment and baseline covariates was used to assess the impact of baseline covariates on treatment success and the incidence of CSF leakage.

In addition all categorical data were summarized by frequencies along with associated percentages for each group. Continuous variables were summarized by number of subjects, mean, standard deviation, minimum, and maximum for each group.

Results

Participant flow

Figure 2 Subject Disposition



Thirteen subjects did not complete the study: 1 subject from the suture treatment group (0.7%) withdrew from the study 13 days post-surgery; 5 subjects (4 from the Evicel group and 1 from the control group, 3.6%) were lost to follow-up; 4 subjects (3 from the Evicel group and 1 from the control group, 2.8%) refused to complete the visit; 3 subjects from the Evicel group (2.1%) did not complete for some "other" reason.

Recruitment

Overall, 194 subjects consented to participate in the study. Of these, 55 subjects were screen failures with 37 subjects (67.3%) failing on inclusion/exclusion criteria.

The study was performed between June 2010 and October 2011 at 14 study sites in UK, Germany, Belgium, Finland, The Netherlands, France, and Australia.

Conduct of the study

Protocol Amendment 01 (dated 19 March 2010) described a change in intrathoracic pressure to be used for the evaluation of intra-operative CSF leakage during the Valsalva maneuver. The pressure to be used was changed from between 20-30 mm Hg (27 - 40 cm H2O) to 20 - 25 cm H2O for 5-10 seconds. This

was in order to use the same pressure as a published trial on which the statistical assumptions for the current study had been made. Furthermore, pediatric subjects were excluded from the study and only subject > 18 years of age could be included.

Protocol Amendment 02 (dated 01 October 2010) described an increase in the number of potential clinical study sites from 15 to 20. Furthermore, it detailed allowing the use of fibrin sealant as a rescue treatment in case watertight closure was not evident after final Valsalva maneuver (treatment failure).

Major protocol deviations are outlined in table 2.

Table 2 Major Protocol Deviations (Study No. 400-09-001)

Subject number	Treatment group	Type of deviation	Comment
14101	EVICEL®	Study procedure	EVICEL® was not applied to the dura[2] defect. The final wound closure used fibrin glue.
15203	EVICEL®	Study procedure	EVICEL® was not applied
23204	EVICEL®	Study procedure	EVICEL® was not applied due to syringe leakage
24102	EVICEL®	Study procedure	SOC treatment and not EVICEL® was applied after subject randomization
24103	EVICEL®	Study procedure	EVICEL® was not applied due to lack of availability
16203	Suture	Study procedure	Post-treatment Valsalva maneuver after closure with sutures was not performed
24101	Suture	Study procedure	SOC (ie sutures, SURGICEL® and ligature) was applied after subject randomization before any Valsalva maneuver
24104	Suture	Study procedure	SOC treatment (ie sutures, SURGICEL® and ligature) was applied before the Valsalva maneuver
21101	EVICEL®	Randomization	A second randomization envelope was opened in error.

Section 16.2.2.1

Baseline data

Table 3 Demographic, baseline and medical history data (FAS)

	EVICEL® N=89	Sutures N=50	Total N=139
Age: y, [median (range)]	56 (20, 78)	59.5 (29, 75)	56 (20, 78)
Gender			
Male	44 (49.4)	23 (46.0)	67 (48.2)
Female	45 (50.6)	27 (54.0)	72 (51.8)
Ethnic group			
White/Caucasian	89 (100)	50 (100)	139 (100)
BMI: [median (range)] kg/m^2	24.6 (17.1, 37.9)	27.0 (17.1, 64.9)	25.7 (17.1, 64.9)
Smoking status [N (%)]			
Current	21 (23.6)	16 (32.0)	37 (26.6)
Former	24 (27.0)	11 (22.0)	35 (25.2)
Never	44 (49.4)	23 (46.0)	67 (48.2)
Medical history			
History of SVT DVT/PE [N (%)]	1 (1.1)	1 (2.0)	2 (1.4)
Family history of DVT/PE [N (%)]†	1 (1.3)	0	1 (0.8)
History of alcohol abuse [N (%)]	2 (2.2)	3 (6.0)	5 (3.6)

† n=76 for EVICEL®; n=42 for sutures; n=118 in total
Table 14.1.2.1, Table 14.1.2.2
Abbreviations: BMI body mass index, DVT deep vein thrombosis, PE pulmonary embolism, SVT superficial vein thrombosis

Table 4 Indication for surgery (FAS)

	EVICEL® n=89 N (%)	Sutures n=50 N (%)	Total n=139 N (%)
Indication for surgery			
Tumor	71 (79.8)	37 (74.0)	108 (77.7)
Aneurysm	9 (10.1)	5 (10.0)	14 (10.1)
Microvascular decompression*	8 (9.0)	4 (8.0)	12 (8.6)
Inflammatory lesions†	1 (1.1)	1 (2.0)	2 (1.4)
Epilepsy	0	1 (2.0)	1 (0.7)
A-V malformation	0	1 (2.0)	1 (0.7)
IV ventricle lesion	0 (0.0)	1 (2.0)	1 (0.7)

Table 14.1.2.5
Abbreviations: A-V arteriovenous
*The indication of microvascular decompression includes those categorized as microvascular decompression, trigeminal neuralgia and hemifacial spasm.
†Patient 12103 had "inflammatory lesions" stated erroneously on the CRF as the reason for surgery. This patient had a tumor at baseline and has not been included in the "tumor" group in this table.

Table 5 Operative parameters (FAS)

	EVICEL® n=89	Sutures n=50	Total n=139
Operative procedure [N (%)]			
Craniotomy	80 (89.9)	46 (92.0)	126 (90.6)
Craniectomy	9 (10.1)	4 (8.0)	13 (9.4)
Type of approach [N (%)]			
Posterior fossa	21 (23.6)	10 (20.0)	31 (22.3)
Supratentorial	68 (76.4)	40 (80.0)	108 (77.7)
CSF leak determination pre-randomization			
Any leak [N (%)]	89 (100)	50 (100)	ND
Spontaneous CSF Leak	67 (75.3)	34 (68.0)	ND
Leak after Valsalva maneuver	22 (24.7)	16 (32.0)	ND
Operation duration [median (range)] (min)	155.5 (50.0, 579.0)	165.0 (64, 448.0)	ND
Time in operating room [median (range)] (min)	229 (103.0, 658.0)	249 (108.0, 534.0)	ND
Procedure to discharge [median (range)] (days)	6 (1, 56)	5 (2, 28)	ND
Admission to discharge [median (range)] (days)	8 (2, 57)	7.0 (2, 34)	ND

Table 14.1.2.5, Table 14.1.3.1, Table 14.1.3.2
Abbreviations: ND not defined; CSF cerebrospinal fluid

Numbers analysed

Overall, 139 subjects were included in the FAS: 89 subjects treated with EVICEL and 50 subjects treated with sutures. There were 6 major effectiveness protocol deviations in the EVICEL treatment group so the PP Set comprised 83 subjects and there were 3 major effectiveness protocol deviations in the suture treatment group so the PP Set comprised 47 subjects.

Outcomes and estimation

Table 6 Subjects receiving rescue therapies (FAS)

	EVICEL® n=89 N (%)	Sutures n=50 N (%)
Number of failures or missing	7 (7.9)	31 (62.0)
Any standard of care method	4 (4.5)	28 (56.0)
Glue		
Duraseal®	0	3 (6.0)
Bioglue®	1 (1.1)	2 (4.0)
Other	1 (1.1)	6 (12.0)
Hemostatic matrix		
SURGICEL®	1 (1.1)	16 (32.0)
Tachosil®	1 (1.1)	0
Gelfoam®	0	4 (8.0)
Other	2 (2.2)	3 (6.0)
Autologous dural patch		
Fascia	1 (1.1)	1 (2.0)
Pericranium	1 (1.1)	2 (4.0)
Muscle	0	1 (2.0)
Biologic dural patch	0	1 (2.0)

Table 14.1.3.7
Note that the percentages in parenthesis have a denominator that relates to the whole FAS for each treatment group

Ten subjects of the 22 subjects deemed study successes in the suture group (45.5%) did receive further adjunctive therapy to provide assurance of the durability of the closure.

Primary endpoint

Intraoperative watertight closure (successes) was achieved in 92.1% of EVICEL-treated subjects (82/89 subjects) versus 38.0% of sutured subjects (19/50 subjects); a treatment difference of 54.1% ($p<0.001$ from both the Fisher's exact test and the Chi-squared test).

Seven subjects (7.9%) from the EVICEL treatment group were considered failures at the primary endpoint as follows:

- Subjects 16201 and subject 19212 were failures for the primary endpoint and all further sensitivity analysis:
    - Subject 16201 had CSF leakage after the second EVICEL application and Valsalva.
    - Subject 19212 had CSF leakage after the first EVICEL application and Valsalva. The investigator deemed the subject a failure after the first EVICEL application and did not administer a second application (this was optional as per protocol).
- Five subjects had missing data and were thus treated as failures for the primary endpoint:
    - Subject 14101 did not receive EVICEL due to a syringe failure
    - Subject 15203 – EVICEL was not used due to an application error

- Subject 23204 – EVICEL was not applied due to device leakage
- Subject 24102 – SOC treatment was applied after randomization, and not EVICEL as per randomization
- Subject 24103 - EVICEL was not available during the procedure

Table 7 Primary effectiveness results

Endpoint (FAS)	EVICEL® n=89 N (%)	Suture n=50 N (%)	Treatment Difference (%)	p-value†	OR CMH (95% CI)
Primary (missing=failure)	82 (92.1)	19 (38.0)	54.1	<0.001	24.87 (8.53, 72.50)
Sensitivity (missing = success)	87 (97.8)	22 (44.0)	53.8	<0.001	57.11 (12.51, 260.68)
Sensitivity (missing = worst case)	82 (92.1)	22 (44.0)	48.1	<0.001	16.53 (6.15, 44.45)
Sensitivity (missing = best case)	87 (97.8)	19 (38.0)	59.8	<0.001	86.31 (17.50, 425.82)
Endpoint (PP Set)	**EVICEL® n=83 N (%)**	**Suture n=47 N (%)**	**Treatment Difference (%)**	**p-value†**	**OR CMH (95% CI)**
Sensitivity (missing = failure)	81 (97.6)	19 (40.4)	57.2	<0.001	69.49 (14.27, 338.39)

Table 14.2.1.1 to Table 14.2.1.4
Abbreviations: OR odds ratio; CMH Cochran Mantel Haenszel
† Fisher's exact and Chi-squared test

Table 8 Intra-operative leakage outcome (FAS)

	N (%)
EVICEL® treatment (n=89)	
Success first application	79 (88.8)
One layer	77 (86.5)
Two layers	2 (2.2)
Success second application	3 (3.4)
Failure: first application; leak post-Valsalva	1 (1.1)
Failure: second application; leak post-Valsalva	1 (1.1)
Unknown wrong method	1 (1.1)
Unknown, no EVICEL® given	4 (4.5)
Suture treatment (n=50)	
Success	19 (38.0)
Failure: spontaneous leak	18 (36.0)
Failure: not water tight†	10 (20.0)
Unknown, wrong method	3 (6.0)

Table 14.1.3.4 and Table 14.1.3.5
†based on leak at the time of post-treatment Valsalva

The results of an exploratory analysis using logistic regression analysis on primary endpoint (FAS with missing data considered failures) with treatment and baseline covariates are presented in Table 11. The odds ratio for the treatment group comparison with BMI included in the model as covariate was OR: 17.12, with 95% CI: (6.47, 45.26). Inclusion of the stratification factor (posterior fossa, supratentorial) in the model: OR: 22.23, 95% CI: (7.55, 65.47) also presented in Table 11.

Primary endpoint analysis – logistic regression with treatment and baseline covariates (FAS; missing=fail)

Endpoint	Model	Effect	Odds Ratio	95% CI for Odds Ratio
Primary endpoint (FAS; missing=fail)	treatment+strata	Treatment: EVICEL vs. Sutures	24.87	(8.53, 72.50)
		Strata:Posterior fossa vs. Supratentorial	0.25	(0.08, 0.82)
	treatment+BMI	Treatment: EVICEL vs. Sutures	17.12	(6.47, 45.26)
		BMI	0.95	(0.87, 1.04)
	treatment+strata+BMI	Treatment: EVICEL vs. Sutures	22.23	(7.55, 65.47)
		Strata:Posterior fossa vs. Supratentorial	4.07	(1.23, 13.43)
		BMI	0.94	(0.85, 1.04)
	treatment+strata+age+smoked + BMI	Treatment: EVICEL vs. Sutures	22.08	(7.44, 65.48)
		Strata:Posterior fossa vs. Supratentorial	4.18	(1.27, 13.83)
		Age	0.98	(0.94, 1.02)
		Ever smoked: Yes vs. No	1.12	(0.42, 2.97)
		BMI	0.94	(0.85, 1.04)

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. The summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9 Summary of Efficacy

Title: A Randomized, Controlled Study to Evaluate the Safety and Effectiveness of EVICEL® as an Adjunct to Sutured Dural Repair	
Study identifier	Protocol Number 400-09-001

Design	Randomized, multi-center, controlled phase 3 study evaluating the safety and effectiveness of EVICEL as an adjunct to sutured dural closure compared to control. Subjects were to undergo an elective cranial surgery of the posterior fossa or supratentorial (craniectomy or craniotomy). Upon completion of the primary sutured dural repair, the closure was to be evaluated for intra-operative cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver 20-25 cm H2O for 5-10 seconds. Subjects who had an identified CSF leak (spontaneous or as identified with the Valsalva) were to be enrolled into the study. Subjects were to be randomized to either EVICEL or to additional repair sutures (control) in a 2:1 allocation ratio and were to be stratified by surgical procedure, posterior fossa or supratentorial. Subjects were to be followed post-operatively through discharge and for 30 days (±3 days) post-surgery. The incidence of CSF leaks was to be assessed within 5 days (±2 days) and 30 days (±3 days) post-operatively as detected by any of the following: clinical observation, diagnostic testing or the need for surgical intervention to treat a CSF leak or pseudomeningocele.			
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	June 2010 to October 2011 not applicable not applicable		
Hypothesis	Superiority			
Treatment groups	EVICEL® group	EVICEL was to be applied to the surgical site by either spraying or dripping onto the dural suture line. n=89		
	Control group	Additional sutures as deemed necessary by the surgeon. n=50		
Endpoints and definitions	Primary efficacy endpoint	Proportion of successes (intra-operative watertight closure) in the treatment of intra-operative CSF leakage. Success was defined as no CSF leakage from dural repair intra-operatively, during Valsalva maneuver 20-25 cm H2O for 5-10 seconds.		
	Safety evaluations	• Incidence of CSF leakage within 5 days (± 2) post-op • Incidence of CSF leakage within 30 days (± 3) post-op • Incidence of adverse events (AE) • Incidence of surgical site infections (SSI) according to National Healthcare • Safety Network (NHSN) criteria within 30 days (± 3) post-op		
Database lock	December 7, 2011			

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Full Analysis Set (FAS)			
Descriptive statistics and estimate variability	Treatment group	EVICEL group	Control group	
	Number of subjects	89	50	

	Intra-operative watertight closure	82/89 (92.1%)	19/50 (38.0%)	
Effect estimate per comparison	Primary endpoint	Comparison groups	EVICEL vs. control	
		Treatment difference	54.1%	
		P-value	<0.001	
Notes	No measures of variability on the original scale are provided with the study report.			

2.4.3. Discussion

Design and conduct of clinical studies

The randomization procedure was comprehensible and sufficiently described.

Due to the nature of the product and the procedures, the study could not be blinded.

Control treatment was defined as “additional dural repair sutures as deemed necessary by the surgeon” thus surgeons were per protocol free to add sutures or not. As there is no common standard treatment for watertight closure of a dura repair suture line, the CHMP had agreed in a Scientific Advice procedure to accept additional sutures as control treatment. Since all the control patients were treated with additional sutures to achieve watertight closure and no protocol violations were observed in relation to additional suturing in the control arm, the choice of control is not considered as a significant source of bias, however there is an uncertainty as to the exact magnitude of the treatment effect, i.e. the difference to the efficacy of the control treatment, in view of several available methods including the use of medical devices or medicinal products such as haemostatic matrix, fibrin sealants, hydrogels or medicated sponges. The fact that there is no consensus on the optimal way to achieve watertight dural closure is clearly reflected in the type of products used for rescue therapy in study 400-09-001.

According to Scientific Advice sought from CHMP in September 2009, it was stated that Evicel would only be applied by dripping and not by spraying, however study protocol allowed for both dripping and spraying and finally Evicel was sprayed in all but one patient. (See discussion on clinical safety).

Intra-operative watertight closure was the primary effectiveness parameter. However, a high clinical relevance is attributed to the post-operative incidence of CSF leakage. This was evaluated as safety parameter within 5 days and within 30 days post-operatively.

Demographics and indication for surgery as well as operative parameters were similar between the two treatment groups. The MAH provided details of discontinued subjects. During their individually shortened follow-up periods either no adverse events were reported or no CSF leak / dural sealing related adverse events.

Efficacy data and additional analyses

Watertight closure as the primary efficacy parameter (successes) was observed in 92.1% of EVICEL-treated subjects (82/89 subjects) versus 38.0% of subjects in the control group (19/50 subjects); a treatment difference of 54.1% ($p<0.001$ from both the Fisher’s exact test and the Chi-squared test).

On the basis of the design of the study submitted, the indication as proposed “tissue glue to promote adhesion/sealing” cannot be supported, as this kind of clinical use has not been investigated. Clinical endpoints from the vascular surgery (data submitted within the original application) and from the neurosurgery study are directly related to “suture support” and not to “adhesion/sealing”. “Tissue gluing”

would include uses in types of neurosurgical procedures which are not covered by this single pivotal study in a strictly defined setting.

Administration of Evicel for example intracerebrally or in spine surgery has not been investigated and is considered to be not covered by the pivotal study. EVICEL is not intended to be used as a glue for the fixation of patches or as a sealant when the dura mater cannot be sutured, as for example in otoneurosurgical or transsphenoidal procedures. These limitations are reflected in the product information as contraindications.

Only adult patients were included in the pivotal study in neurosurgery. Evicel is not indicated in children.

The dose to be applied for adjunctive use of Evicel to suture repair of dura mater in neurosurgery was up to 8 ml and this is reflected in the posology section.

Subjects were excluded from the study when implants from synthetic materials or dural patches were used for dural repair. The exclusion was made in order to ensure that the target area being evaluated for efficacy was as homogeneous as possible within the study setting. The SmPC reflects that there is no experience of such usage by a relevant warning in section 4.4.

The benefit of a surgical technique or treatment is not only based on the intra-operative performance but also on the post-operative course. The higher incidence of post-operative CSF leakage in Evicel-treated subjects compared to control is discussed in the clinical safety section.

Therefore the indication was revised as: EVICEL is also indicated as suture support for haemostasis in vascular surgery and for suture line sealing in dura mater closure.

2.4.4. Conclusions

In study 400-09-001, a clear superiority of Evicel over control treatment in terms of the primary endpoint has been shown.

As available data do not justify a general indication to neurosurgery as applied for, the indication was specified to “suture line sealing in dura mater closure”.

The posology is stated under 4.4 of the SmPC as: “for suture line sealing in dura mater closure, doses of up to 8 ml were used”.

Appropriate contraindications were included in the SmPC in order to reflect the use in the clinical trial setting. Moreover in section 4.4 of the SmPC lack of data on the concomitant use of EVICEL for dural suture line sealing with implants from synthetic materials or dural patches was reflected.

Information on trial 400-09-01 has been included in section 5.1 as” The efficacy of EVICEL for suture line sealing in dura mater closure was demonstrated in 139 patients (89 treated with EVICEL and 50 controls) undergoing craniotomy/craniectomy procedures.”

2.5. Clinical Safety aspects

2.5.1. Introduction

Evicel has first been approved in the EU in October 2008 with the indication as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis and also as suture support for haemostasis in vascular surgery. Evicel can be dripped or sprayed with pressurized gas.

Clinical studies to support the above indication were performed in Retroperitoneal or Intra-Abdominal Surgery (400-05-006), in Vascular Surgery (400-05-001)and in Neurosurgery (400-09-001).

As a condition of approval, Omrix committed to conduct a Post-Authorization Safety Study (PASS) in vascular surgery. The recommendation was that this should be an observational, non-interventional study of approximately 300 patients with submission of safety data at every 100 patients. The first interim analysis, conducted after enrolment of 100 patients, has now been completed and does not reveal any safety concerns associated with the use of the product in the approved indication (study 400-08-004).

The most important safety issue during the post-marketing phase was the risk of air embolism associated with the spray application of the product, which was assessed through an Article 20 of Regulation (EC) No 726/2004 triggered by the EC on the occurrence of five cases of life-threatening air embolism (of which two had a fatal outcome) reported. As a result risk management activities were implemented.

Patient exposure

Overall, during the clinical development of Evicel, a total of 421 subjects were included in randomized, controlled clinical trials, 230 of which were treated with Evicel and 191 of which were included in the control groups. Each subject was exposed to a single dose of Evicel (between 0.5 and 10 mL of combined product).

In the present pivotal study 400-09-001 to support the neurosurgical indication applied for, a total of 139 subjects were randomized to treatment, thereof 89 to Evicel and 50 to control.

Safety Endpoints

Incidence of CSF leakage within 5 days

One subject (1.1%) in the EVICEL treatment arm, and no subjects in the suture treatment arm had CSF leakage within 5 days of the procedure:
- Subject 10101 had CSF leakage on Day 4. A single additional suture was given the same day and CSF leakage resolved within 2 days.

Incidence of CSF leakage within 30 days

By 30 days post-procedure, a CSF leakage was reported in a further 6 subjects in the Evicel treated group, all assessed as possibly related to the study treatment:

small CSF leak	4 days from treatment
chronic subdural hygroma	21
hydrocephalus	1
CSF leakage through nose	2

CSF leak	7
CSF nasal leak	6

Based on the data from the AE Listings, the post-operative leakage after treatment was 6/89,(6.7%) with Evicel and 1 in the control arm (1/50, 2.0%).

Incidence of surgical site infections (SSI)

Surgical site infections were defined according to CDC/NHSN criteria described in the protocol. One subject from each treatment group experienced a SSI (subject 23202 from the EVICEL treatment group and subject 23101 from the control group), both had meningitis. Both SSIs were classified as space/organelle infections defined as infections that appeared to be related to the operation.

Adverse events

All AEs were to undergo medical review for determination of those considered related to dural-sealing. These may include, but are not limited to the following:

1. If the CSF is leaking externally, it can be:
    - Otorrhea
    - Rhinorrhea
    - Incisional leaks
2. If the CSF is collected, it can be:
    - Subcutaneous collection
    - Subdural hygroma
    - Pseudomeningocele
3. Others:
    - Hydrocephalus
    - Meningitis: a potential consequence of CSF leaks, in particular external leakage.

The incidence of subjects who experienced at least one AE was comparable between treatment groups: 176 AEs in 57 subjects (64.0%) who had been treated with EVICEL and 83 AEs in 31 subjects (62.0%) who had (additional) suture treatment.

The most frequent AEs were headache, hypertension, hypotension, nausea, vomiting, respiratory failure and swelling, all commonly associated with this type and complexity of surgery. The incidence of these AEs was comparable between both treatment groups.

Table 10 Number of patients experiencing any AE, SAE, Severe AE or AR requiring treatment during Evicel study 400-09-001 in neurosurgery

Variable	EVICEL (n=89)	Control (n=50)
Total number of AEs	176	83
Number of patients with at least one in the following categories:		
AE	57 (64.0%)	31 (62.0%)
SAE	10 (11.2%)	4 (8.0%)
Severe AE	5 (5.6%)	0 (0.0%)
AE requiring medical/surgical action	50 (56.2%)	29 (58.0%)
Related or possibly related AE	7 (7.9%)	2 (4.0%)
Related or possibly related SAE	4 (4.5%)	1 (2.0%)
Dural sealing-related AE	7 (7.9%)	2 (4.0%)

Table 11 Evicel study 400-09-001 in neurosurgery; Adverse Events that occurred in at least 5% of patients in a treatment group

System Organ Class	Preferred Term	Number (%)	
		EVICEL (n=89)	Control (n=50)
Gastrointestinal Disorders	Nausea	9 (10.1)	3 (6.0)
	Vomiting	9 (10.1)	1 (2.0)
General Disorders & Administration Site Conditions	Swelling	4 (4.5)	5 (10.0)
Nervous System Disorders	Headache	17 (19.1)	6 (12.0)
Respiratory, Thoracic and Mediastinal Disorders	Respiratory Failure†	4 (4.5)	4 (8.0)
Vascular Disorders	Hypertension	12 (13.5)	8 (16.0)
	Hypotension	6 (6.7)	1 (2.0)

†Verbatim term: respiratory insufficiency

Overall, 7 EVICEL subjects (7.9%) and 2 suture subjects (4.0%) experienced AEs considered possibly related to the study product. These included intracranial hypotension (CSF leakage), CSF rhinorrhea, meningitis, chemical meningitis, headache, hydrocephalus, subdural hygroma, and hematoma.

Table 12 Adverse events with a causal relationship to product

System Organ Class	Preferred Term	Number (%)	
		EVICEL (n=89)	Control (n=50)
Gastrointestinal Disorders	Nausea	9 (10.1)	3 (6.0)
	Vomiting	9 (10.1)	1 (2.0)
General Disorders & Administration Site Conditions	Swelling	4 (4.5)	5 (10.0)
Nervous System Disorders	Headache	17 (19.1)	6 (12.0)
Respiratory, Thoracic and Mediastinal Disorders	Respiratory Failure†	4 (4.5)	4 (8.0)
Vascular Disorders	Hypertension	12 (13.5)	8 (16.0)
	Hypotension	6 (6.7)	1 (2.0)

†Verbatim term: respiratory insufficiency

Table 13 Summary of dural-sealing related AEs (Safety Analysis Set)

System Organ Class	Preferred Term	Number (%)	
		EVICEL (n=89)	Control (n=50)
Gastrointestinal Disorders	Nausea	9 (10.1)	3 (6.0)
	Vomiting	9 (10.1)	1 (2.0)
General Disorders & Administration Site Conditions	Swelling	4 (4.5)	5 (10.0)
Nervous System Disorders	Headache	17 (19.1)	6 (12.0)
Respiratory, Thoracic and Mediastinal Disorders	Respiratory Failure†	4 (4.5)	4 (8.0)
Vascular Disorders	Hypertension	12 (13.5)	8 (16.0)
	Hypotension	6 (6.7)	1 (2.0)

†Verbatim term: respiratory insufficiency

Serious adverse event / deaths / other significant events

There were no deaths and no suspected unexpected serious adverse drug reactions (SUSAR).

A total of 17 SAEs were reported during study 400-09-001; 12 SAEs were reported in 10/89 patients in the EVICEL group (11.2%) and 5 SAEs were reported in 4/50 patients in the control group (8.0%). The only SAE that occurred in more than one subject was meningitis which occurred in one subject in the EVICEL group and one in the control group.

Four events in the EVICEL group (meningitis, subdural hygroma, hydrocephalus, and CSF rhinorrhea) and one in the control group (meningitis) were considered by the sponsor to have a potential relationship to the study treatment.

Table 14 Subjects experiencing SAEs (Safety Analysis Set)

System Organ Class	Preferred Term	Number (%)	
		EVICEL (n=89)	Control (n=50)
Gastrointestinal Disorders	Nausea	9 (10.1)	3 (6.0)
	Vomiting	9 (10.1)	1 (2.0)
General Disorders & Administration Site Conditions	Swelling	4 (4.5)	5 (10.0)
Nervous System Disorders	Headache	17 (19.1)	6 (12.0)
Respiratory, Thoracic and Mediastinal Disorders	Respiratory Failure†	4 (4.5)	4 (8.0)
Vascular Disorders	Hypertension	12 (13.5)	8 (16.0)
	Hypotension	6 (6.7)	1 (2.0)

†Verbatim term: respiratory insufficiency

Laboratory findings

Laboratory parameters (electrolytes, blood urea nitrogen, creatinine, complete blood count, liver function test and any others routinely requested by the investigator) were measured within 24 hours prior to surgery, 5 (±2) days post-surgery and at 30 (±3) day follow-up.

Four EVICEL subjects and one control group subject had clinically significant abnormalities in laboratory tests at Day 5 post-surgery. These included hypokalemia (2 subjects), hyponatremia (1 subject), increased ALT (1 subject) and elevated liver enzymes (1 subject). They each corresponded with a reported AE that was considered non-serious and unrelated to study treatment. All AEs had resolved by the end of the study, with the exception of one subject in the EVICEL treatment group who had ongoing elevated liver enzymes at last contact. There were no clinically significant abnormalities reported at Day 30.

Post marketing experience

Data from previous studies with Quixil and Evicel, were resubmitted but not discussed in the context of this indication.

The most significant safety issue in the postmarketing setting was the recent issue of life-threatening events of air/gas embolism reported associated with spray application with Evicel, including two fatal events which was assessed as part of an Article 20 of Regulation (EC) 726/2004.

Safety in special populations

No paediatric data are submitted.

Investigations of safety in other safety populations were not submitted.

Safety related to drug-drug interactions and other interactions

No such investigations were submitted.

Discontinuation due to adverse events

Reasons for discontinuations were presented in the Clinical efficacy section. No discontinuation was on safety grounds.

2.5.2. Discussion on clinical safety

In the present study 89 subjects were randomized to treatment with Evicel and 50 to control. Both treatments were adjunctive to primary suture dura repair.

The most frequent AEs were headache, hypertension, hypotension, nausea, vomiting, respiratory failure and swelling, which are all commonly associated with this type of surgery. Nausea, vomiting and headache were more frequently reported in the Evicel group.

A higher incidence of dural-sealing related events was reported in the treatment group: 7 EVICEL subjects (7.9%) and 2 suture subjects (4.0%) had dural-sealing related AEs. From the EVICEL treatment group these included CSF leakage (2 subjects), CSF rhinorrhea (2 subjects), meningitis (1 subject), subdural hygroma (1 subject), and hydrocephalus (1 subject). From the suture treatment group CSF leakage plus meningitis (1 subject) and chemical meningitis (1 subject) were reported. Excluding the cases of meningitis, which are not necessarily related to a CSF leak, the remaining AEs are explicitly or potentially related to a CSF leak in 6/89 (6.7%) subjects in the Evicel group and 1/50 (2%) subject of the control group. This difference is considered to be clinically relevant.

Following analyses of narratives of subjects who had dural-sealing related AEs, it can be concluded that the event of subdural hygroma and the hydrocephalus may not have been caused by a cerebrospinal fluid leakage, so as far as these two events are concerned, however, there are two cases of nasal leakage of CSF (CSF rhinorrhea), for which should be considered to be post-operative CSF leak events. Thus in total, four cases of CSF leakage in subjects treated with Evicel (4/89, 4.5%), thereof two as CSF leak with impaired wound healing and two as CSF rhinorrhea, in comparison to one case of CSF leak in the suture control group (1/50, 2.0%). Postmarketing pharmacovigilance reporting will be monitoring dural sealing related adverse events.

Subjects with gaps at the durotomy edges were excluded from the trial. A gap that is too large cannot be adequately treated using a sealant, it requires additional sutures. In addition there is the risk that gas or EVICEL could pass the suture line creating a pneumocephalus (asymptomatic intracranial air). Gaps at the

durotomy edges and holes within the suture line are considered to be a risk when applying Evicel by spraying with pressurized gas, as there might be the risk of blowing air/gas or fibrin sealant through such holes in the subarachnoidal space. The definition of the maximum gap size as 2 mm was based on published information from previous clinical studies[2]. A risk assessment was made and as a result, the existence of gaps and holes of greater than 2 mm after primary dural closure was translated in a contraindication in Section 4.3 of the SmPC, stating that EVICEL must not be used when gaps of greater than 2 mm remain after dural closure.

The risk of venous gas embolism, when administering Evicel with pressurized gas in neurosurgery, was discussed. As the indication was restricted to suture line sealing in dura mater closure and it is contraindicated to use Evicel in the presence of gaps in the dural suture line of greater than 2 mm, moreover a warning has been added that complete haemostasis should be achieved before application of Evicel to seal the dural suture line; these measures are regarded to adequately eliminate the risk of venous gas embolism when using Evicel in this new indication.

Subjects planned to receive radiation therapy to the head within 7 days after surgery were excluded from the study. The reason for this exclusion criterion was that, although radiation therapy 7 days after surgery is atypical of surgical practice, there was a concern that radiation therapy could affect the quality of the dura. The impact on a dural closure by sealant where the surgical defect is exposed to radiation therapy has not been evaluated. The lack of data is reflected as a warning in SmPC section 4.4:
This is considered to appropriately reflect the lack of knowledge in patients with radiotherapy following use of Evicel for dural suture line sealing.

Nausea, vomiting and headache were more frequently reported in the Evicel group. These events are common postoperative events in cranial neurosurgery. In the limited study sample no statistically significant difference was found in the frequency of these events compared to control treatment. Monitoring of these events in the post-marketing is implemented in the RMP.

2.5.3. Conclusions

In study 400-09-001 involving 139 patients undergoing elective neurosurgical procedures (89 treated with EVICEL and 50 controls), a total of 7 subjects treated with EVICEL experienced nine AEs that were considered to be possibly related to the study product. These included intracranial hypotension (CSF leakage), CSF rhinorrhea, meningitis, headache, hydrocephalus, subdural hygroma, and haematoma.

Adverse events reported in this study were as expected in this kind of surgical interventions. The incidence of CSF leakage and the incidence of Surgical Site Infections were monitored as safety endpoints in the study. At 30 days post-operatively the incidence of SSIs was similar between the two treatment groups. Post-operative CSF leakage occurred within 30 days from treatment in 4/89 (4.5%) subjects treated with EVICEL (two cases of CSF leakage with impaired wound healing and two cases of rhinorrhoea) and in 1/50 (2.0%) subjects treated with additional sutures. The above information is included in section 4.8 of the revised SmPC.

As the indication was finally restricted to suture line sealing in dura mater closure, the risk of unsafe use in neurosurgery settings outside of the studied population is eliminated. For this purpose contraindications were agreed under section 4.3 of the SmPC to state that:

- EVICEL must not be used for sealing the suture line in dura mater if there are gaps of greater than 2 mm remaining after suturing.
- EVICEL must not be used as a glue for the fixation of dural patches.
- EVICEL must not be used as a sealant when the dura mater cannot be sutured.

In addition the following warnings under section 4.4 of the SmPC are implemented:

- The concomitant use of EVICEL for dural suture line sealing with implants from synthetic materials or dural patches has not been evaluated in clinical studies.
- The use of EVICEL in patients undergoing radiotherapy within 7 days after surgery has not been evaluated. It is not known whether radiation therapy could affect the efficacy of fibrin sealant when used for suture line sealing in dura mater closure.
- Complete haemostasis should be achieved before application of EVICEL to seal the dural suture line.
- The use of EVICEL as a sealant in transphenoidal and otoneurosurgical procedures has not been studied.

The incidence of nausea, vomiting or headache are to be monitored as part of the routine post-marketing PhV and reported in PSURs. Post-operative CSF leakage and other dural sealing related AEs are also addressed appropriately in the RMP and monitored and reported within pharmacovigilance reporting.

2.5.4. PSUR cycle

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

The next data lock point is on 8 June 2014.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

Based on the PRAC review of the Risk Management Plans version 9 date 8 March 2013, the PRAC considers by consensus that the risk management system for the sealant solution on Human Fibrinogen and Human Thrombin (EVICEL) as a supportive treatment in surgery or for the proposed indications (as a tissue glue to promote adhesion/sealing, or as suture support in vascular surgery and in neurosurgery and surgical procedures where contact with cerebro-spinal fluid or dura mater can occur) could be acceptable provided an updated risk management plan and satisfactory responses to the questions detailed below are submitted:

Conclusions on the safety specification

1 "Product embolism" could be misinterpreted and the MAH should use the term of "thromboembolism" or "gas embolism" to differentiate between these two types of events.

2 "Details of important identified and potential risks from clinical development" is missing. The MAH is asked to add the clinical studies with their potential risks.

3 Actions taken by regulatory authorities and/or marketing authorisation holder for safety reasons: The attachment should include the DHPC, conditions and other educational measures (labels and

tag on regulator and applicator, warning card). 'Recommendation for CO2 only…' should be amended to reflect that use of CO2 is mandatory, rather than a recommendation.

4 The missing information items "risks when applied through a flexible endoscope", "risks when used for gastrointestinal anastomosis", "risks in patients intolerant to heparin" and "risks in re-vascularisation using autologous conduits or prosthetic material other than uncoated or heparin-coated PTFE" are missing and should be added, given the lack of data.

5 Study 400-11-002 should be added as PASS. Cumulative review in all PSURs and –as applicable- analysis in the PASS should be included as routine pharmacovigilance measure for all safety concerns.

6 Also as routine pharmacovigilance measure the following sentence should be included:

The MAH continues to monitor and analyze all cases of special interest as follows:
- off-label ophthalmic use
- Lack of Efficacy reports
- Thromboembolic events
- Air/Gas Embolism

- **Conclusion of the suggestions which concern the quality of the RMP**

7 Concerning table 1 to 9 an additional table specified by dose should be added. In table 2 and 5 the last row should be split in rows 75-84 and 85+.(Section 1.2.1)

8 The MAH has stated that market research has been also conducted by surgical specialty. It would be useful to have such information being provided in the RMP and to include it in addition to the new Table (Section 1.2.1).

9 The interim analysis of the study 400-09-001 should be added as annex.

10 The MAH should add more details concerning study 400-08-004, such as title objectives safety concerns addressed, status and date for submission of interim or final reports in a table. In addition study 400-11-002 has to be described and added.

11 "Details of important identified and potential risks from clinical development and post-authorisation experience", the percentage 68.7% is not straightforwardly related to the number of patients enrolled in clinical trial; instead it might be supposed to be wrongly related to the number (183) of adverse events. Maybe it would be useful to write "46 out of [denominator]".

12 "Details of important identified and potential risks from clinical development and post-authorisation experience": The MAH should present the name and number of the clinical studies where the events were observed. The clinical studies in annexes 3 and 4 should be replaced by the template tables. It should be described also if the study is completed, ongoing or planned with the resp. time-table.

13 "Important identified risk": the content concerning the cases of gas/air embolism should be replaced by the template table. All cases should be summarized.. Four cases (OMX-2008-00043, OMX-2009-00011, OMX-2009-00036 and OMX-2010-00001) were previously assessed and formed the basis of the risk mitigation activities (DDL and revised safety warning) executed between August and October 2010. To give a complete overview these cases should also be described.

14 According to the recommendation of the CHMP the MAH is requested to change the post-authorisation development plan by adding a warning card that informs about the correct pressures and distances for the spray application for open and laparoscopic procedures. The requested time table should be considered and target completion date has to be adopted in accordance with the CHMP recommendation.

Within three months (as of March 2013) the users of the spray application of this product should be provided with:

- labels for the pressure regulator that inform about the correct pressures and distances in open and laparoscopic procedures;

- a warning card that informs about the correct pressures and distances for the spray application for open and laparoscopic procedures;

- a yellow tag, to be placed on the device air hose, which provides instructions for use. If the tag is provided as part of the medicinal product, it should be incorporated in the product information via a variation procedure.

Concerning the planned action "Pressure Regulator design change to limit upper spray limit" the MAH should add the maximum pressure at 1.7 bars.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Air/gas embolism
	Lack of efficacy
Important potential risks	Hypersensitivity/allergic reactions, including severe anaphylaxis
	Graft occlusion
	Graft infection
	Product embolism
	Medication error
	Tissue adhesion
	Denaturation in contact with antiseptics
	Off-label use in children and adolescents
	Off-label use of spray application in endoscopic surgery
Missing information	Use in children and adolescents
	Use in women who are pregnant or lactating

Pharmacovigilance plans

Table 2.2: On-going and planned studies in the PhV development plan

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
A Prospective, Single-Arm, Observational, Non-interventional Study for EVICEL Fibrin Sealant (Human) when used as an Adjunct to Haemostasis in Vascular Surgery	Quantify frequency of graft occlusion in vascular surgeries using Evicel	Graft occlusion	Started	Next interim reports planned July 2013, Final study report February 2016

Risk minimisation measures

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
1. Air or Gas embolism	Revised text in SPC as follows: Section 4.2 The use of EVICEL is restricted to experienced surgeons who have been trained in the use of EVICEL. To avoid the risk of potentially life threatening air embolism EVICEL should be sprayed using pressurised CO2 gas only. Prior to applying EVICEL the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices). The product should only be reconstituted and administered according to the instructions and with the devices recommended for this product. See Sections 4.4 and 6.6 for specific spray recommendations on the required pressure and distance from tissue per surgical procedure and length of application tip Section 4.3 Spray application of EVICEL should	• Use of CO2 only as the gas vehicle during spray application of Evicel • Direct to Healthcare Professional Communication • Updated product training program • Redesign of pressure regulator

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	not be used in endoscopic procedures. For laparoscopy, see Section 4.4 Section 4.4 Life threatening air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer EVICEL. EVICEL should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process. Air or gas embolism has occurred with the use of spray devices employing pressure regulator to administer EVICEL. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. EVICEL spray application should only be used if it is possible to accurately judge the spray distance, especially during laparoscopy. Spray distance from tissue and pressure should be within the ranges recommended by the manufacturer (see table in Section 6.6 for pressure and distance). When using accessory tips with this product, the instructions for use of the tips should be followed EVICEL should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process Section 6.6 To avoid the risk of life-threatening air embolism EVICEL should only be sprayed using pressurized CO2 When applying EVICEL using a spray device, be sure to use a pressure and a distance from the tissue within the ranges recommended by the Manufacturer.	
2. Rare occurrence of Hypersensitivity/allergic reactions	Contraindication in section 4.3 of SmPC stating: *Hypersensitivity to the active substances or to any of the excipients*	None
3. Isolated occurrence of severe anaphylaxis, especially if the preparation is applied repeatedly, or administered to patients known to be	Warning in section 4.4 of SPC stating: *As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
hypersensitive to constituents of the product.	*reactions include hives, generalized urticaria, tightness of the chest, wheezing, hypotension (anaphylactoid syndrome) and anaphylaxis. If these symptoms occur, the administration should be immediately discontinued. In case of shock, standard medical treatment for shock should be implemented. Since anaphylaxis is a rare event without known predisposing factors the routine surveillance will be through the education of all HCP who use the product to report any event using the PV system. The relationship of such an event to the potential product immunogenicity will be assessed by the HCP.*	
4. Complications related to graft occlusion and/or graft infection and/or thromboembolic events could potentially occur, due to the nature of the product. This should be observed particularly in cases of vascular surgery.	HCP will be instructed to report immediately any graft occlusion and/or graft infection as potential adverse events is provided under "undesirable effects" in section 4.8 of the SmPC. The prevalence rate of thromboembolic events (TEE) not related to intravascular injection is unknown; however complications related to TEE are common in hospitalized surgical patients. Any reports of complications related to TEE events will be closely monitored categorized and identified as special interest cases. These "special interest cases" will be highlighted within the Periodic Safety Update Reports (PSURs)	None
5. Tissue adhesion and Associated complications	Warning in section 4.4 of the SmPC 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*	None
6. Incorrect mixing of the components that could lead to a lack of clotting of the product, resulting in lack of efficacy.	The correct handling and use of the product is provided in section 6.6 of the SmPC (instructions for use), in the instructions for use and the applicator device package.	None
7. Inadvertent intravascular injection may also occur and could lead to thromboembolic event and DIC, and there is also a risk of anaphylactic reaction	• Contraindication in section 4.3 of SmPC stating that EVICEL must not be applied intravascularly and about hypersensitivity to active substances • Warning in section 4.4 of SmPC stating: *For epilesional use only.* • Warning in section 4.4 of SmPC stating: *Do not apply*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	intravascularly. Life threatening or thromboembolic complications may occur if the product is applied intravascularly. • Undesirable effects in section 4.8 of SmPC listing potential reaction due to intravascular injection and hypersensitivity reactions.	
8. Antibodies against components of fibrin sealant/haemostatic products may occur rarely.	Undesirable effects in section 4.8 of SmPC listing potential hypersensitivity and allergic reactions as well as the possible development of antibodies against components of fibrin sealants.	None
9. Transmission of infectious agents	Warning in section 4.4 of SmPC 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. 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 anaemia).* *It is strongly recommended that every time EVICEL is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.*	None
10. Uncommon or rare adverse reactions may have not been seen because of the small size of	None	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
population exposed in clinical trials. Experience in larger populations is currently missing.		
11. Use in paediatrics	Section 5.1 Pharmacological Properties of the SmPC defines that data is too limited to support the safety and effectiveness of EVICEL in children	None
12. Use in pregnant or lactating patients	Warnings in section 4.6 pregnancy and lactation of the SmPC states that the use in human pregnancy or during breast feeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and post-natal development. Therefore, the product should be administered to pregnant and lactating women only if clearly needed	None

The CHMP endorsed this advice without changes.

2.7. Changes to the Product Information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.8, and 5.1 of the SmPC have been updated. The new indication was reflected in section 4.1 of the SmPC. Particularly, new contraindications have been added to section 4.3 of the SmPC. Posology recommendations and warnings related to the new indication have been updated in sections 4.2 and 4.4 of the SmPC, accordingly. The newly identified ADRs, as well as safety information from the pivotal 400-09-001 study were included in section 4.8 of the SmPC. The pivotal efficacy information from the pivotal 400-09-001 study was included in section 5.1 of the SmPC.

In line with the changes in the SmPC, changes to the Package Leaflet sections 1, 2 and 4 have been applied.

Changes were also made to the PI to bring it in line with the current QRD template, version 9.0, which were reviewed and accepted by the CHMP.

3. Overall conclusion and impact on the benefit/risk balance

Beneficial effects

There is a clear numeric superiority of Evicel over control treatment. Intra-operative watertight closure (successes) was achieved in 92.1% of subjects randomized to treatment with Evicel (82/89 subjects)

versus 38.0% of control subjects (19/50 subjects); a treatment difference of 54.1% ($p<0.001$) indicated the superiority of EVICEL over control which was additional sutures if deemed necessary.

Uncertainty in the knowledge about the beneficial effects

Subjects who were scheduled to receive radiation therapy of the head within 7 days following the surgery, were excluded from the study. It is thus unknown, whether radiation would have an impact on the dura closure by the fibrin sealant. However, most of the patients have cranial surgery for a tumor (78% of subjects in this study), which may also require radiation therapy. This lack of data is reflected as a warning in SmPC section 4.4.

Subjects were excluded from the study when implants made of synthetic materials or dural patches were used, which are part of standard treatment for the closure of durotomies. It has therefore not been investigated, whether Evicel and those implants or patches can be used together. At present, it cannot be excluded that the polymerized layer of Evicel may negatively interfere with the sealing effect and the healing process of such implants and dural patches. The lack of knowledge in these settings is also reflected in the SmPC section 4.4.

Risks

Unfavourable effects

Adverse events reported in this study were as expected for this kind of surgical interventions.

Nausea, vomiting and headache were reported in a slightly higher percentage of subjects treated with Evicel than with control, but following additional analyses these differences were not considered statistically significant.

Seven subjects randomized to Evicel treatment (7.9%) and 2 subjects randomized to control treatment (4.0%) had AEs which were assessed as related to dural sealing. AEs directly or potentially related to a CSF leak were more frequently reported in the Evicel group than in the control group: The number of AEs of CSF leakage is in the Evicel group and in the control group. In the Evicel treatment group 4/89 (4.5%) subjects experienced CSF leakage/CSF rhinorrhea, 1 subject subdural hygroma, and 1 subject a hydrocephalus. From the suture treatment group only one event of CSF leakage (1/50; 2.0%) was reported. Cases of subdural hygroma and hydrocephalus were confirmed not related to CSF leakage.

Five of the dural-sealing related AEs in subjects of the Evicel group had to be treated in the post-operative period by a surgical intervention, compared to only one subject in the control arm requiring a surgical intervention for CSF leak.

Uncertainty in the knowledge about the unfavourable effects

The small number of patients might not address clinically relevant safety issues.

In all but one subjects, Evicel application was by spraying which uses pressurized gas. A dura suture, which is leaking cerebrospinal fluid, is not watertight in the outer direction, but is also not airtight in the inner direction into the CSF space. The application of pressurized gas may be associated with the risk that gas could enter the cerebrospinal fluid space. A pneumatocephalus with increased intracranial pressure could consequently occur. Gaps and holes in the suture line are considered to bear the risk of insufflation.

Similar to a potential risk of insufflation, there may be a risk of spraying fibrin particles or fibrin thrombi in the subdural and the CSF space. Subjects having a gap between durotomy edges of greater than 2 mm after primary closure were excluded from the study. Under study conditions this was cautiously managed, but it is unclear, whether all surgeons will always be aware of this potential risk.

These risks were reflected in the following contraindications: "*EVICEL must not be used for suture line sealing in dura mater when gaps of greater than 2 mm remain after dural closure*." and "EVICEL must not be used as a sealant when the dura mater cannot be sutured". In addition, a warning has been added stating that "*Complete haemostasis should be achieved before application of EVICEL to seal the dural suture line.*" Other potential risks discussed are addressed in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Post-operative cerebrospinal fluid (CSF) leakage may lead to life-threatening complications and it is therefore of major clinical importance to reduce the risk of CSF leakage in neurosurgery. It is commonly accepted that intra-operative watertight closure of the dura is the optimal prophylaxis against the occurrence of post-operative CSF leaks. Clinically more relevant than the immediate intra-operative watertight closure is that the closure of the dura is stable and maintained during the healing period, thus avoiding the occurrence of a post-operative CSF leakage and associated complications. Evicel treatment has demonstrated to be effective in this sense.

The incidence of post-operative CSF leakage was 4/89 (4.5%) in the Evicel group and 1/50 (2.0%) in control. Post-operative CSF leakage and dural-sealing related AEs are addressed appropriately as identified risks in the RMP.

The incidence of adverse reactions was as expected in this neurosurgery setting. Dural-sealing related events will be monitored as identified risk within post-marketing pharmacovigilance reporting.

Benefit-risk balance

There is a clear beneficial effect with regard to the primary effectiveness parameter in this special setting of the pivotal study.

The favourable effects are considered to more than exceed the unfavourable effects/uncertainties and overall the benefit risk profile in the restricted indication of "suture line sealing in dura mater closure" is considered to be positive.

Discussion on the benefit-risk balance

The use of a fibrin sealant as a "second line treatment" to tighten the dura after durotomy in elective cranial surgery, when primary dura suture repair did not provide a watertight closure is for the intention to reach a stable and durable closure of the dura mater, thus preventing the occurrence of a post-operative CSF leakage, which is a major and potentially life-threatening complication of neurosurgery.

In this pivotal study, Evicel has demonstrated superiority over additional sutures when applied.

The incidence of adverse reactions was as expected in this neurosurgery setting. Dural-sealing related events will be monitored as identified risk within post-marketing pharmacovigilance reporting.

4. Recommendations

The application for the extension of indication as revised in line with the discussion above is approvable since major objections and other concerns have all been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include: use for “suture line sealing in dura mater closure” for Evicel.
As a consequence, update of sections 4.1, 4.2, 4.3, 4.4, 4.8, and 5.1 of the SmPC in order to relevant posology, contra-indications, warnings, safety information. The Package Leaflet is updated in accordance.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

Minor editorial amendments were also implemented in the PI.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

References

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