HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

4 November 2009

EVICEL, solution for sealant
Box containing 2 x 1 mL bottles (CIP: 575 463-7)
Box containing 2 x 2 mL bottle (CIP: 575 464-3)
Box containing 2 x 5 mL bottle (CIP: 575 466-6)

Applicant: ETHICON

Component 1: Human clottable protein containing mainly fibrinogen and fibronectin
Component 2: Human thrombin

ATC Code: B02BC

List I - for hospital use only

Date of marketing authorisation (centralised procedure): 06/10/2008

Reason for request: Inclusion on the list of medicines approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 PROPERTIES OF THE MEDICINAL PRODUCT

1.1. Active substance

Component 1: Human clottable protein containing mainly fibrinogen (50-90 mg/mL) and fibronectin, with no bovine aprotinin

Component 2: Human thrombin (800-1200 IU/mL)

1.2. Indications

"EVICEL is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis (see section 5.1).
EVICEL is also indicated as suture support for haemostasis in vascular surgery. "

1.3. Dosage

"The volume of EVICEL to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.
The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.
Application of the product must be individualised by the treating physician. In clinical trials in vascular surgery, the individual dosage used was up to 4 ml, whereas in retroperitoneal or intra-abdominal surgery the individual dosage used was up to 10 ml. However, for some procedures (e.g. liver traumata) larger volumes may be required.
The initial volume of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary."

2 COMPARABLE MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

B: Blood and blood forming organs
B02: Antihaemorrhagics
B02B: Vitamin K and other haemostatics
B02BC: Local haemostatics

2.2. Medicines in the same therapeutic category

Comparator medicines

Other sealants indicated as supportive treatment in surgery to improve haemostasis and/or support sutures in vascular surgery:

BERIPLAST, powders and solvents for sealant
Beriplast can be used locally as supportive treatment where standard surgical techniques are insufficient:
- for improvement of haemostasis (including endoscopic treatment of bleeding gastroduodenal ulcer)
- as a tissue to promote adhesion/sealing or as suture support.

QUIXIL, solutions for sealant
Quixil is used as supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis.
Efficacy has been demonstrated in liver surgery and orthopaedic surgery (see section 5.1 of SPC).

TISSUCOLKIT, powders, solutions and solvents for fibrin sealant~~, for~~ epilesional use
Supportive treatment designed to promote local haemostasis during surgery.

2.3. Medicines with a similar therapeutic aim

TACHOSIL, medicated sponge
TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis,to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient (see section 5.1).

Non-drug treatments with "medical device" status also exist.

3 ANALYSIS OF AVAILABLE DATA

The efficacy and safety of EVICEL have been evaluated in two randomised open-label studies:

- study 400-05-006: in retroperitoneal and intra-abdominal surgery (planned urology, general/gastrointestinal and gynaecology procedures) in comparison with an active comparator agent (SURGICEL);

- study 400-05-001: in vascular surgery in comparison with manual compression, which is a standard haemostasis technique.

3.1. Efficacy

Study 400-05-006

The primary objective of this multi-centre, randomised, open-label study involving 135 patients undergoing retroperitoneal and intra-abdominal surgery was to demonstrate non-inferiority of EVICEL in comparison with a medical device based on oxidised cellulose (SURGICEL)1.

Inclusion criteria:
- children and adults undergoing planned retroperitoneal and intra-abdominal surgery. Procedures were required to include (but were not limited to) the following interventions, which involve varying levels of haemorrhage risk:

urology: simple or radical nephrectomy, adrenalectomy, radical prostatectomy, pyeloplasty;

gynaecology: hysterectomy, ovarian cystectomy, lymphadenectomy;

general surgery: colectomy with or without anal anastomoses, lower anterior resections, abdominoperineal resections.

target operation site consisting of soft tissue with slight to moderate bleeding and for which conventional techniques (e.g. suture, ligature, cauterisation) were ineffective or impractical.

Treatments:

Patients were randomised after identification of the target haemorrhagic operation site:
- EVICEL arm: 2 x 5 mL as drops or spray
- SURGICEL arm: 10.2 x 20.3 cm.

Additional application of one of these treatments was allowed during the 10-minute observation period.

Primary endpoint: successful haemostasis, defined by the absence of bleeding at the target operation site with no use of additional haemostasis measures (other than EVICEL and SURGICEL), 10 minutes after randomisation.

EVICEL was to be non-inferior if the lower limit of the 95% CI of the ratio of the percentage success rate in the EVICEL arm : percentage success rate in the SURGICEL arm was greater than 0.8.

[1] An absorbable contact haemostasis product, which has a primarily mechanical action. Indication in the CE mark: use in surgical procedures as a support treatment to help to control bleeding from capillaries, veins and small arteries when ligature or the usual methods of bleeding control are impractical or ineffective.

The statistical analysis plan also provided for subsequent superiority analysis if the lower limit of the 95% CI were to be greater than 1.

Secondary endpoints:

- absence of bleeding at the target operation site at 4 and 7 minutes after randomisation;
- time (absolute) to achievement of haemostasis;
- percentage treatment failure, defined as the presence of bleeding 10 minutes after randomisation or the appearance of brisk bleeding within the 10 minutes following randomisation requiring the administration of additional haemostasis measures;
- complications that were potentially linked to bleeding (after 7-14 days of follow-up).

Results:
The median age was higher in the EVICEL arm than in the SURGICEL arm (57.3 vs 53 years). Of the 135 patients who were included, 4 children aged 16 or under were treated with EVICEL, and 7 with SURGICEL.
Slight bleeding was more common in the EVICEL arm (see table 1).
The quantity of EVICEL used was between 0.5 and 10 mL (median 5 mL) and of SURGICEL 1-300 cm2 (median 187.5 cm2). Rates of additional application were similar in the two arms.

Table 1: Characteristics of patients and procedures (study 400-05-006)

N = 135 (ITT)	**EVICEL N = 66**	**SURGICEL N = 69**
Median age (years)	57.3	53
Mean duration of procedure (min)	195.1	213
Type of surgery (% of patients):		
- urology	41.8	36.8
- gynaecology	31.3	29.4
- general surgery	26.9	33.8
Intensity of bleeding (% of patients):		
- mild	61.2	52.9
- moderate	38.8	47.1
Initial haemostasis methods (% of patients):		
- cauterisation;	50.7	72.1
- suture;	16.4	14.7
- other methods (clips, pressure or argon-beam coagulation)	14.9	13.2
- ligatures	4.5	7.4
- none of these methods (as impractical)	32.8	19.1

Absence of bleeding (primary endpoint) at the target operation site 10 minutes after randomisation was observed in 95.2% of patients in the EVICEL arm and in 80% of patients in the SURGICEL arm (RR = 1.19, 95% CI [1.05; 1.39] in the PP population). Similar results were observed for the ITT population (RR = 1.18, 95% CI [1.04; 1.36]).
The lower limit of the 95% CI of the relative risk (1.05) was greater than the predefined threshold of 0.8.
As a result, EVICEL was demonstrated to be non-inferior to SURGICEL in terms of haemostasis success at 10 minutes.

As the lower limit of the relative risk confidence interval was greater than the threshold of 1 as laid down in the protocol (1.04), a superiority analysis was carried out: At 10 minutes after randomisation, haemostasis had been obtained in 95.5% (63/66) of patients in the EVICEL arm versus 81.2% (56/69) of patients in the SURGICEL arm ($p<0.05$) on ITT analysis.

Secondary endpoints (ITT):

- At 4 minutes, haemostasis had been achieved in 75.8% of patients in the EVICEL arm and in 53.6% of patients in the SURGICEL arm (RR = 1.41, 95% CI [1.10; 1.86]).
At 7 minutes, haemostasis had been achieved in 90.9% of patients in the EVICEL arm and in 76.8% of patients in the SURGICEL arm (RR = 1.18, 95% CI [1.02; 1.40] in the ITT population).

- Median time to haemostasis was 2.51 minutes for EVICEL versus 4 minutes for SURGICEL, a difference of 1.5 minutes (log-rank, p<0.001).

- Rates of complication potentially linked to haemorrhage were 10.6% (7/66) patients in the EVICEL arm versus 15.9% (11/69) in the SURGICEL arm (NS).

- Treatment failure was observed in 3 of the 66 patients in the EVICEL arm (4.5%) and in 13 of the 69 patients in the SURGICEL arm (18.8%).

Study 400-05-001

Multi-centre, randomised, open-label study involving 147 patients undergoing vascular surgery with PTFE grafts[2] to carry out end-to-side femoral artery anastomosis or upper extremity arterial anastomosis to provide vascular access for haemodialysis.

The primary objective of this study was to evaluate the efficacy of EVICEL in comparison with manual compression in terms of time to haemostasis.

Inclusion criteria:

- adults aged over 18 years;
- elective vascular surgery with at least one end-to-side anastomosis or upper extremity vascular access arterial anastomosis using uncoated or heparin-coated PTFE grafts associated with sutures.

Treatments:

Patients were randomised if bleeding persisted in spite of the fact that the anastomosis line was secure:
- group 1: EVICEL spray (n=75)
- group 2: manual compression (n=72)

Primary endpoint: efficacy of haemostasis at 4 minutes, defined as the absence of bleeding at the anastomosis site 4 minutes after randomisation.

Secondary endpoints:

- efficacy of haemostasis 7 and 10 minutes after randomisation;
- percentage of patients with complications potentially linked to bleeding on follow-up up to 5 weeks after the procedure;
- percentage treatment failure, defined as the presence of bleeding 10 minutes after randomisation or the appearance of severe bleeding within the 10-minute observation period requiring the administration of additional haemostasis measures.

Results:

Over 60% of patients were aged between 50 and 74. Demographic characteristics were similar in the two arms.

[2] PTFE: polytetrafluoroethylene

64% of patients (48/75) in the EVICEL arm underwent femoral artery procedures, and 70.8% (51/72) in the manual compression arm. An upper extremity vascular access procedure- were carried out in 36% of patients in the EVICEL arm and in 29.2% of patients in the manual compression arm.
The majority of patients in the EVICEL arm received 4 mL of the product.

At 4 minutes after randomisation, haemostasis (primary endpoint) had been achieved in 85.3% of patients in the EVICEL arm and in 38.9% of patients in the manual compression arm (OR = 11.3, 95% CI [4.7; 27.5] in the ITT analysis).
Results obtained for femoral artery procedures and upper extremity vascular access were similar.
Percentage achieving haemostasis at 7 minutes was 90.7% in the EVICEL arm and 59.7% in the manual compression arm (OR = 7.9, 95% CI [2.8; 21.9]).
Similar results were observed at 10 minutes (96% in the EVICEL arm and 69.4% in the manual compression arm; OR = 11.3, 95% CI [3.7; 91.8]).
No difference was observed between the EVICEL and manual compression arms in terms of the percentage of patients with complications potentially related to bleeding (anaemia, haematoma, bleeding, increased drainage, bruising, seroma): 12/75 or 16%, vs 15/72 or 20.8%, NS.
Treatment failure was observed in 6 patients in the EVICEL arm (8%) and in 23 of the manual compression arm (31.9%), (OR=0.14, 95% CI [0.05; 0.45], p=0.001). Treatment failure was primarily caused by persistence of bleeding beyond the 10-minute observation period (4% in the EVICEL arm vs 30.6% in the manual compression arm).

3.2. Adverse effects

Safety data are taken from clinical studies and international pharmacovigilance data; EVICEL has been marketed in the United States since September 2006.

Study 400-05-006

The percentage of patients with at least one adverse event was similar in the two treatment arms (68.7% for EVICEL and 70.6% for SURGICEL).
Serious adverse events were reported in 12 patients in the EVICEL arm (16 events, of which one led to death) and in 15 patients in the SURGICEL arm (18 events).
Three serious adverse events (one abdominal abscess in the EVICEL arm and one abdominal abscess and one pelvic abscess in the SURGICEL arm) were considered likely to have a causal link with the study treatment.
The most frequent serious adverse events were: urine retention, abdominal abscess, paralytic ileus (1 case reported for each arm).

Study 400-05-001

The percentage of patients with at least one adverse event was similar in the two treatment arms (64.0% for EVICEL and 70.8% for manual compression).
Serious adverse events were reported in 23 patients in the EVICEL arm (31 events) and in 21 patients in the manual compression arm (29 events). These events led to 2 deaths in each arm.
In the EVICEL arm, adverse events considered likely to have a causal link with the study treatment were reported in 9 patients: graft infection, graft occlusion, slight superficial groin wound dehiscence, staphylococcal infection, femoral graft infection, haematoma and oedema of the arm, reduced haemoglobin levels, inguinal haematoma, bleeding and haematoma of the abdominal incision, bilateral dehiscence of the inguinal incisions.

The most frequently reported serious adverse events were:
- in the EVICEL arm: graft thrombosis, haemorrhage at incision site, respiratory failure, graft infection;
- in the manual compression arm: graft occlusion, respiratory failure, hypotension, peripheral ischaemia, heart failure, prosthesis infection.

In both arms, eight patients had graft thrombosis or occlusion during the study (5-week observation period). However, the risk was greater during the first 12 postoperative days in the EVICEL arm: 4 patients in the EVICEL arm and 2 patients in the manual compression arm were considered to have early graft thrombosis after the procedure.
Of the 8 patients in each arm, repeat surgery was required for 7 patients in the EVICEL arm and 3 in the manual compression arm.
An observational study (Post-authorisation safety surveillance or PASS) is planned for around 300 patients undergoing vascular surgery, as part of the risk management plan, in order to evaluate in particular the incidence of thrombosis (including graft thrombosis) and haemorrhage events linked to the target bleeding operation site.

Potential risks of fibrin-based haemostasis agents (data taken from SPC)

"Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatics. In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product. Mild reactions can be managed with anti-histamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

Antibodies against components of fibrin sealant/haemostatic products may occur rarely.

Inadvertent intravascular injection could lead to thromboembolic event and DIC, and there is also a risk of anaphylactic reaction (see 4.4).

For safety with respect to transmissible agents, see 4.4. "

Pharmacovigilance data: PSUR (United States) covering the period 1 September 2006 to 31 March 2008

Over this period, 81,448 kits were sold in the United States and 3 serious adverse events involving EVICEL were reported: 1 cerebrovascular accident and 2 cases of fluid retention (in the abdomen and spinal column).

3.3. Conclusion

The efficacy and safety of EVICEL were evaluated in two randomised open-label studies involving patients for whom conventional surgical techniques were inadequate.

It has been demonstrated that EVICEL is non-inferior to SURGICEL (oxidised cellulose) in terms of absence of bleeding (primary endpoint) 10 minutes after randomisation (95.2% vs 80%; RR = 1.19 95%CI [1.05-1.39] in PP) in the improvement of haemostasis in cases of slight to moderate bleeding when conventional surgical techniques are inadequate in retroperitoneal and intra-abdominal surgery.

The efficacy of EVICEL in comparison with manual compression in suture support in vascular surgery has been demonstrated: 4 minutes after randomisation, haemostasis (primary endpoint) had been achieved in 85.3% of patients in the EVICEL arm versus 38.9% of patients in the manual compression arm (OR = 11.3, 95% CI [4.7; 27.5] in the ITT analysis).

In both studies, no difference was observed between the EVICEL and SURGICEL or manual compression arms in terms of complications that were potentially linked to haemorrhage.

The percentage of patients with at least one adverse event was similar in the EVICEL and control arms.
Aside from the potential risks of fibrin-based haemostasis agents, no safety concerns were identified in the study involving retroperitoneal and intra-abdominal surgery.

In the study involving vascular surgery, thrombosis or graft occlusion was reported in 8 patients in each groups, including early thrombosis (EVICEL: 4/75 patients vs manual compression: 2/72 patients; NS).
Repeat surgery was required for 7 patients in the EVICEL arm and 3 in the manual compression arm.
These results, which were observed when evaluating a small number of subjects (147 patients were randomised) do not enable any conclusions to be drawn as to a causal link with the treatment. A follow-up safety study involving a larger number of patients undergoing vascular surgery, as part of the risk management plan, in order to evaluate in particular the incidence of thrombosis (including graft thrombosis) and haemorrhage events linked to the target bleeding operation site.

The data in children are too limited to support the efficacy and safety of EVICEL in children.

There are no studies comparing EVICEL with other treatments to support conventional haemostasis methods, other than SURGICEL.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The conditions for which EVICEL is indicated can be life-threatening

The efficacy of this support treatment has been demonstrated in retroperitoneal and intra-abdominal surgery and in vascular surgery. The efficacy/adverse effects ratio is high.

This is a support treatment that is designed to be curative.

This product is a second-line treatment in surgery for improvement of haemostasis where standard surgical techniques are insufficient, and as suture support for haemostasis in vascular surgery.

Public health benefit:
Haemorrhage is a significant factor in postoperative complications and mortality during surgery. Significant haemorrhages do not require support treatment for haemostasis. In terms of public health, the burden represented by haemorrhage requiring support treatment to achieve haemostasis can be considered to be low.
In view of the available data (haemostasis success at a given moment), and in the absence of comparative data versus other fibrin sealants, the performance of EVICEL in comparison with other available fibrin sealants has not been established.
In addition, the clinical result also depends on the type of surgery and the surgeon's mastery of the relevant surgical technique.
Fibrin sealants may contribute to a reduction in post-operative mortality, but the impact of EVICEL in terms of morbidity (reduction in drainage duration, transfusion requirements, length of hospital stay and frequency of repeat intervention) or mortality has not been studied.
As a result, EVICEL is not likely to provide a benefit to public health.

There are other drug and non-drug treatments.

The actual benefit is substantial.

4.2. Improvement in actual benefit

EVICEL does not provide an improvement in actual benefit (IACB V) in comparison with other support treatments in surgery when conventional techniques are inadequate and to support sutures. EVICEL does increase haemostasis success rates in retroperitoneal and intra-abdominal surgery and in vascular surgery, but it does not alter rates of complications linked to haemorrhage and there are no comparisons available with treatments to support conventional haemostasis methods (other than SURGICEL).

4.3. Therapeutic use

The objective of haemostasis treatment administered during surgical procedures is to limit blood loss and the risk of postoperative complications and to reduce transfusion requirements.

The level of haemostasis is determined primarily by the surgical technique used and by the surgeon's mastery of the particular surgical procedure.

In addition to conventional haemostasis methods, support treatment may be necessary, particularly in emergency situations.

The type of haemostasis used depends on the type of surgery, the location, the type of bleeding and the surgeon's experience.

EVICEL is indicated as supportive treatment in surgery for improvement of haemostasis where standard surgical techniques are insufficient, and as suture support for haemostasis in vascular surgery.

The efficacy of EVICEL in terms of achievement of haemostasis has been demonstrated in a non-inferiority study involving 3 types of surgery (urological, gynaecological and general) carried out on soft tissue with slight to moderate bleeding and in which conventional techniques (e.g. suture, ligature, cauterisation) had proved to be ineffective or impractical. In line with EMEA guidelines (2004)[3] concerning haemostasis treatments in surgery, the use of EVICEL may be extended to surgery involving all organs, with the exception of surgical procedures for which specific data are awaited:

- neurosurgery;
- gastrointestinal anastomoses;
- application via a flexible endoscope to treat bleeding;
- surgery in which fibrin sealant is used as a tissue adhesive (e.g. in pulmonary surgery).

EVICEL has also been shown to be effective in suture support in vascular surgery involving insertion of a PTFE graft to carry out end-to-side femoral artery anastomosis or arterial anastomosis for upper extremity vascular access for haemodialysis.

Given the available data, and the lack of a comparison with support treatments other than SURGICEL, EVICEL is an alternative to other surgical haemostasis techniques in the improvement of general haemostasis and to support vascular sutures when conventional techniques are inadequate, with the exception of neurosurgery, gastrointestinal anastomoses, application via flexible endoscope to treat bleeding and use as tissue adhesive, for which situations specific data are awaited.

[3] http://www.emea.europa.eu/pdfs/human/bpwg/108900en.pdf

4.4. Target Population

The population in whom EVICEL would be used consists of patients undergoing:
- a surgical procedure for which additional haemostasis measures are required, when conventional techniques (sutures, clips, argon-beam coagulation) have proved inadequate;
- vascular surgery requiring suture support to achieve haemostasis.

The data in children are too limited to support the efficacy and safety of EVICEL in children. There is insufficient relevant data to support the use of EVICEL to promote tissue sealing, in neurosurgery, via a flexible endoscope to treat bleeding or for gastrointestinal anastomoses.

There are no data in the literature concerning the proportion of cases of haemorrhage that require additional haemostasis measures for any given surgical procedure. It is therefore difficult to estimate the precise number of patients who could benefit from EVICEL for each type of surgical procedure.

It should be noted that only experienced surgeons should use EVICEL.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage given in the Marketing Authorisation.

The committee wishes to emphasise that it is likely to re-evaluate EVICEL in view of the conclusions of re-assessment of surgical haemostasis agents.