FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: November 30, 2007

FROM: Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch, Division of Hematology, OBRR

SUBJECT: STN 125010/105, OMRIX biopharmaceuticals, LTD. EVICEL Fibrin Sealant (Human)
Clinical efficacy Supplement
Final Review Memo

TO: Debbie Cordaro, RPM, Division of Blood Applications, OBRR

THROUGH: Toby Silverman, MD, Chief, Clinical Review Branch, Division of Hematology, OBRR

Summary

EVICEL fibrin sealant is currently indicated for use as an adjunct to hemostasis in patients undergoing liver surgery when control of bleeding by conventional surgical techniques is ineffective or impractical. This efficacy supplement contains an integrated summary of effectiveness, integrated summary of safety and the final study report entitled, "A Prospective, Randomized, Controlled Evaluation of Fibrin Sealant 2 (FS 2) as an Adjunct to hemostasis for Soft Tissue Bleeding During Retroperitoneal or Intra-abdominal Surgery". The phase III pivotal study in soft tissue bleeding was conducted to support a general adjunct to hemostasis indication for EVICEL.

The study in soft tissue bleeding was conducted at 18 study centers in the US (16 study centers recruited subjects). The objective of the study was to evaluate whether the fibrin sealant, FS 2 (EVICEL) was non-inferior to Surgicel in achieving hemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery. The primary endpoint was hemostatic success, defined as absence of bleeding at the target bleeding site at 10 minutes following randomization to treatment.

The study met its primary endpoint, non-inferiority for FS2 in control of bleeding at 10 minutes. The adverse event profile is not unusual for this surgical patient population. There was no overall imbalance in adverse events or serious adverse events between the two groups although there were a few imbalances in particular adverse events listed according to MEDRA terminology.
On 20 September 2007, FDA issued an information request letter to Omrix. The letter requested that Omrix submit updated labeling for Evicel (to include the vascular adjunct to hemostasis indication obtained in 2006 and also to submit all case report forms. The revised labeling was received on October 4, 2007. A separate labeling review has been submitted to this efficacy supplement file. In November 2007 Omrix inquired about including ---------- procedures as part of Evicel's indication for an adjunct to hemostasis in general surgery. I have recommended that Omrix propose language to include

---------- procedures in their label. Since there is no change to the formulation of Evicel for ---------- procedures and there are no safety concerns outside the scope of what is already in the Evicel label regarding Evicel's administration in surgical procedures, I find the proposal to include ---------- general surgical procedures to be an acceptable indication.

The case report forms were reviewed and there are no comments to be conveyed to the sponsor about the forms.

Trial Design
Title:
"A Prospective, Randomized, Controlled Evaluation of Fibrin Sealant 2 (FS 2) as an Adjunct to hemostasis for Soft Tissue Bleeding During Retroperitoneal or Intra-abdominal Surgery".

Objectives:
Primary

- Evaluate whether the fibrin sealant, FS2, was non-inferior to Surgicel in achieving hemostasis during surgical procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgery.

Secondary

- Absence of bleeding at the soft tissue TBS at 4 and 7 minutes following randomization
- Absolute time to hemostasis (TTH)
- Incidence of treatment failure
- Incidence of potential bleeding related complications to end of follow-up
- Adverse events to end of follow-up.

Study design:
Phase III, prospective, randomized controlled clinical study to evaluate the safety and efficacy of fibrin sealant, FS2 efficacy was evaluated by assessment of procedures involving soft tissue bleeding in retroperitoneal and intra-abdominal surgeries. Subjects were stratified by age (16 years old or less and over 16 years old) in order to comply with the Pediatric Research equity Act (PREA). The study population included patients undergoing non-emergency retroperitoneal or intra-abdominal surgery in which a soft tissue target bleeding site (TBS) was identified for treatment with an adjunct to hemostasis.

Subjects were screened up to 3 weeks prior to surgery. Physical examinations and complete blood counts (CBC) and coagulation profiles (i.e. PT, PTT) were assessed prior to surgery. Subjects were reviewed at a baseline time assessment within 24 hours of surgical procedure.

Surgical procedures were performed according to standard of care. The TBS was identified as a site with challenging bleeding for which topical hemostatic adjuncts to hemostasis were deemed appropriate for use. The TBS was identified during the retroperitoneal or soft tissue dissection related to the primary operative procedure. It was the first site in the soft tissue identified with mild to moderate bleeding, where conventional methods for obtaining hemostasis were ineffective or impractical. and an adjunct to hemostasis was required. The TBS was the only soft tissue site or region to be evaluated for hemostasis; parenchymal or anastomotic bleeding sites were not included.

Once the TBS was identified, the subject was randomized, the TBS was treated according to the randomization schedule and then time to hemostasis was observed.

Time was recorded for both Surgical and FS 2 according to the following table:

T_0	Start time when randomization envelope was opened
T_1	Time when FS2 application was completed
T_4	Bleeding assessment at 4 minutes post randomization
T_7	Bleeding assessment at 7 minutes post randomization
T_{10}	Bleeding assessment at 10 minutes post randomization
TTH	Absolute TTH was recorded

* Note: Re-application of product (FS-2 and Surgicel) was permitted at the surgeon's discretion within the 10 minute observation period.

Main Criteria for inclusion:

1. Patients requiring non-emergent retroperitoneal or intra-abdominal surgical procedures in surgical specialties shown below. Procedures included, but were not limited to, the following:

Urology	Gynecology	General Surgery
Simple or radical Nephrectomy	Radical hysterectomy	Coloectomy with or without Anal anastomosis
Adrenalectomy (open)	Radical cystectomy (bladder removal)	Low anterior resections
Radical prostatectomy	Lymphadenectomy	Abdominoperineal resections
Pyeloplasty	Primary tumor reduction Surgery (i.e. ovarian cancer surgery)	Retroperitoneal tumor resection Surgery

2. Presence of an appropriate soft tissue TBS identified intraoperatively by the surgeon
3. Patients were willing to participate in the study and had provided written informed consent.

Exclusion Criteria:

- Emergent procedure
- Parenchymal or anastomotic bleeding sites
- Intraoperative finding s identified by surgeon that may have precluded conduct of study procedure
- Known intolerance to blood products or to one of the components of the study drug

• Patients unwilling to receive blood products
• Patients with autoimmune deficiency
• Known current alcohol and / or drug abuse
• Participation in another investigational drug or device research study within 30 days of enrollment

Treatments:
Subjects were randomized to receive a single use treatment of either the investigational product, FS2, or the control treatment, Surgicel. Surgicel is an oxidized, regenerated cellulose hemostat. It is indicated for use as an adjunct to hemostasis in surgery.
FS 2 is provided as a kit containing 2 separate boxes: one box containing the 2 components in separate vials (2 x 5 mL) and a second box with the device package containing the equipment necessary for application of the product. The 2 components are: 1. Biological Active Component 2 (BAC 2) containing Human Fibrinogen 55-85 mg/ mL. 2. Thrombin containing Human Thrombin 800-1200 IU/mL and calcium chloride.

Duration of treatment:
FS2 (2 x 5 ml) was applied to the TBS immediately after opening the randomization envelope. Re-application of the product was allowed at the surgeon's discretion within the 10 minute observation period.
Surgicel was applied to the TBS immediately after opening the randomization envelope, Reapplication was allowed at the surgeon's discretion within the 10 minute observation period.

Schedule of Study Assessments:

Procedures	Screening[a]	Baseline (w/in 24 hrs prior to procedure	Surgical Procedure	Post Surgery to Hospital Discharge[b]	> 7 to 14 days F/U
Inclusion/ Exclusion	X	X	X		
Informed consent	X				
Demographics	X				
Medical History	X	X			
Concomitant Medications[C]		X	X	X	X
Physical Exam	X				
CBC w/ diff	X			X	
Coagulation (PT,PTT, INR)	X			X	
Procedures	Screening[a]	Baseline (w/in 24 hrs prior to procedure	Surgical Procedure	Post Surgery to Hospital Discharge[b]	> 7 to 14 days F/U

Inclusion/ Exclusion	X	X	X		
Informed consent	X				
Demographics	X				
Medical History	X	X			
Concomitant Medications[c]		X	X	X	X
Physical Exam	X				
CBC w/ diff	X			X	
Coagulation (PT,PTT, INR)	X			X	
Heparin admin./ Reversal			X		
Randomization			X		
Product Application			X		
Intra-op Details			X		
Determination of hemostasis at TBS			X		
Use of other hemostatic measures			X		
Bleeding related Complications				X	X
Adverse events			X[d]	X	X

a Within 21 days of procedure
b Within 24 hours prior to discharge
c Topical hemostats and chronically taken medication
d Starting from point of randomization

Criteria for evaluation:
The primary effectiveness variable was hemostasis outcome at 10 minutes with success defined as the absence of bleeding and no treatment with any hemostatic measures other than the assigned hemostatic adjunct, FS2 or Surgicel, at 10 minutes following randomization. All other subjects were considered to be failures.

Secondary effectiveness variables:

- Absence of bleeding at the TBS 4 and 7 minutes following randomization. Subjects receiving additional hemostatic measure within the 10 minute observation period were considered failures.
- Incidence of potential bleeding related complications
- Incidence of treatment failure defined as either a.) presence of bleeding at the TBS 10 minutes following randomization or b.) occurrence of brisk bleeding which required the administration of additional hemostatic measures during the 10 minute observation period.

TTH was also recorded using actual time for an exploratory survival analysis.

Safety variables:

- Coagulation parameters (PT, PTT, INR)
- CBC
- Adverse events

Statistical Analysis Plan

Sample size

The sample size estimate was based on the assumption that the hemostatic success rate in the FS and Surgicel groups would be 90%.

Analysis Sets:

ITT- all randomized subjects. This set was further analyzed according to age:

a.) Adult ITT (all randomized subjects > 16 yrs and < 65 yrs)

b.) Adult 65+ ITT (all randomized subjects aged 65 years or more)

c.) Pediatric ITT (all randomized subjects aged 16 or less) with the following subgroups:

- Neonates (birth to one month)
- Infants (one month to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16 years)

Per protocol (PP) -subjects in the ITT set who had no major protocol violations (defined as a violation affecting the primary parameter). Treatment allocation was based on planned treatment

Safety analysis set- all subjects who were randomized and received treatment

The sponsor analyzed absence of bleeding at the TBS at 4, 7, and 10 minutes following randomization, incidence of treatment failures, and incidence of potential bleeding related complications.

The proportion of subjects achieving hemostatic success was calculated by treatment group. A 2- sided 95% confidence interval (CI) for the ratio of proportions of success was constructed. If the lower limit of the CI was greater than 0.80, then non-inferiority is claimed. It should be noted that the final statistical analysis plan tests FS 2 for non-inferiority to Surgicel. However, in the event that the lower limit of the 95% CI is greater than 0.8 **and** greater than 1.0, then superiority is claimed at the 5% statistical significance level ($p < 0.05$). In this later case, the p-value associated with the test of superiority would be calculated.

Survival methods using Kaplan Meier curves were used to analyze TTH. Included in this model

were treatment, center and age (≤ 16, ≥ 16). No analysis of safety variables was done.

Adverse event data were described using summary descriptive statistics.

Study Population
One hundred thirty five subjects were consented, enrolled and randomized into the study- 66 to FS2 and 69 to Surgicel.

Four subjects withdrew prior to study completion: 3 from the FS 2 group (subject 22008- death 8 days post op, subject 26014 – unable to reach by phone for post op follow-up, and subject 26019 –limited post op follow-up. One subject (# 26018) from the Surgicel group withdrew due to lost to follow-up.

One subject (# 22003) was randomized to Surgicel; however, the subject received FS2.

Protocol Deviations:
There were a total of 124 protocol deviations affecting 37 (55.2%) of the FS2 subjects and 50 (73.5%) Surgicel subjects. The most common deviation was due to "study procedure" violations (i.e. visits outside of the protocol schedule or laboratory parameters that were not obtained as scheduled by the protocol). Seven subjects (3 in the FS2 group and 4 in the Surgicel group) had protocol deviations due to the randomization process.

Eight protocol deviations (5 in the FS 2 group and 3 in the Surgicel group) resulted in the exclusion of subjects from the per protocol analysis set. Noted is that subject 22003 was randomized to Surgicel, but received FS 2 in error. This subject is counted in the Surgicel group for the ITT analysis (randomized) and in the FS2 group for safety (as treated).

Subject	Treatment	Deviation	Details
16008	FS2	Randomization	Randomization envelope 16007 skipped
---------	FS2, peds	Randomization	Randomization envelope --------- skipped
13402	Surgicel, peds	Randomization	Randomization envelope 13401 skipped
19004	FS2	Study procedure	Fibrin sealant applicator not prepared until just before use
20001	FS2	Study procedure	Delay after opening randomization envelope and prior to applying product
18001	Surgicel	Randomization	Delay after opening randomization envelope and prior to applying product
18002	Surgicel	Randomization	Delay after opening randomization envelope and prior to applying product
22003	FS2	Randomization	Subject 22003 was randomized to Surgicel, but received FS 2 in error.

Efficacy Results:
The study was conducted at 16 sites. One hundred thirty five (135) subjects [67 subjects- FS2 and 68 subjects Surgicel] were enrolled and randomized and included in the intent to treat (ITT) analysis. The 135 subjects included

- 11 pediatric subjects aged 16 years or less: 4 FS2 and 7 Surgicel
- Adult analysis set included 72 subjects aged 17 to 64: 32 FS 2 and 40 Surgicel
- Adult analysis set aged 65 years and older : 30 FS2 and 22 Surgicel

One hundred twenty seven subjects [62 FS2 and 65 Surgicel] were included in the per protocol (PP) analysis.

According to the sponsor, there was an imbalance in treatment for the pediatric group (4 FS2 and 7 Surgicel, in part due to the following:
a.) low recruitment within centers resulting in incomplete blocks randomized and
b.) skipped randomization numbers in two of the centers.

Demographics:
FS2 and Surgicel groups were similar in demographic characteristics. Randomization was stratified by age (≤ 16, > 16). The pediatric subgroups are as follows:
Infants: 1 month to 23 months: 1 subject --------- (Surgicel)
Children: 2 to 11 years: 2 subjects --------- and ---------- (FS2)
4 subjects ---------, ---------,---------, --------- (Surgicel)

Adolescents: 12-16 years: 2 subjects ---------, --------- (FS2)
2 subjects ---------, --------- (Surgicel)

Surgical procedures:
Surgical procedures were similar for both treatment groups; however, urological procedures were more commonly performed in the FS 2 group. Bleeding at the TBS was classified as mild for 61.2% of FS2 subjects and 52.9% of Surgicel subjects. The number of re-applications of product was similar for the FS2 and Surgicel groups, with 82% of subjects needing only one application, 15% needing 2 applications and 4% requiring 3 applications.

Primary efficacy analysis:
More subjects in the FS2 group than in the Surgicel group achieved hemostasis at 10 minutes (95.5% versus 81.2%) The proportion of success in the FS 2 group compared with the success in the Surgicel group (relative risk) is 1.18 with 95% CI of 1.04 to 1.36. As prospectively defined in the statistical analysis plan, since the lower 95% CI exceeds 80%. FS2 is non-inferior to Surgicel. Additionally, the lower 95% CI also exceeds 1.0 and therefore, superiority of FS2 over Surgicel has been demonstrated according to the protocol definition.

Table 4: Hemostasis at 10 minutes:

Variable	FS2	Surgicel	RR	95% CI for RR
Hemostasis at 10 Minutes:				
ITT set	63/66 (95.5%)	56/69 (81.2%)	1.18	1.04, 1.36
PP set	59/62 (95.2%)	52/65 (80%)	1.19	1.05, 1.39
Adult set	32/32 (100%)	32/40 (80%)	---	
Adult 65+ set	27/30 (90%)	19/22 (86.4%)	---	
Pediatric set	4/4 (100%)	5/7 (71.4%)	---	

The age subsets in pediatric subjects show similar efficacy results to the adult population. In the ITT analysis, success tended to be 90-100 % for the FS 2 group and somewhat lower (71-86%) for the Surgicel group

Table 5: Actual times to hemostasis for pediatric subjects:

Pediatric Subgroup	Subject Number	Treatment	TTH (minutes)	Comments
Infants	---------	Surgicel	15.00	Failure*
Children	---------	FS2	1.48	
	---------	FS2	3.03	
	---------	Surgicel	3.17	
	---------	Surgicel	13.08	Failure*
	---------	Surgicel	1.35	
	---------	Surgicel	5.92	
Adolescents	---------	FS2	0.73	
	---------	FS2	1.88	
	---------	Surgicel	2.92	
	---------	Surgicel	6.53	

*Treatment failures were defined as either:

- Presence of bleeding at the TBS 10 minutes following randomization (defined as TTH exceeding 10 minutes) or
- Brisk bleeding occurred requiring the need to administer additional hemostatic measures during the 10 minute observation period (defined as bleeding complications by 10 minutes)

According to study protocol, the sponsor was to have a planned logistic regression analysis looking at treatment, center (centers 14,18 and 25 combined into one center- called center 99), age (pediatric, adult and adults 65+) and treatment / center interaction.
This analysis was not done because according to the sponsor, the model fit was questionable due to low numbers of subjects per center and because pediatric subjects were only recruited at a few centers.

Given the slight imbalance in terms of TBS bleeding severity, an additional analysis was

conducted to evaluate success of FS2 and Surgicel in mild or moderate bleeding conditions. Evaluation of TTH by TBS severity indicated that the observed success rates were slightly better for mild bleeding (100% in the FS2 group verse 89.2% in the Surgicel group) and for moderate bleeding at the TBS success rates were 88.5% for FS2 and 71.9% for Surgicel.

Secondary Efficacy Endpoints

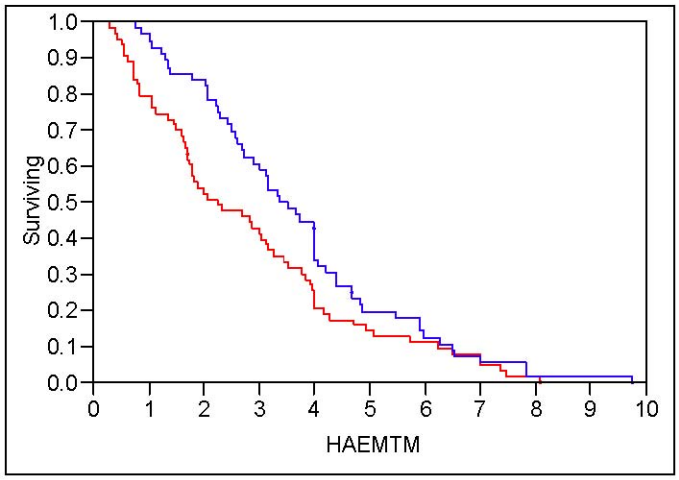
TTH at 4 and 7 minutes

Time to hemostasis was evaluated at 4 and 7 minutes in addition to the landmark 10 minutes. The following table captures the results of the 4 and 7 minute TTH efficacy in the two treatment groups:

Variable	FS2 (n= 66)	Surgicel (n=69)	RR [1]	95% CI for RR
Hemostasis ≤ 4 minutes	50 (75.8%)	37 (53.6%)	1.41	1.10, 1.86
Hemostasis ≤ 7 minutes	60 (90.9%)	53 (76.8%)	1.18	1.02, 1.40
Potential bleeding related Complications [2]	7 (10.6%)	11 (15.9%)	0.67	0.28, 1.56
Treatment failure:	3 (4.5)	13 (18.8)		
TTH > 10 minutes Brisk bleeding complications by 10 minutes	3 (4.5%) 0 (0.0%)	9 (13.0) 4 (5.8%)	0.35 1.06 [3]	0.10, 1.13 1.00, 1.16
TTH <10 minutes			**LR** [4]	
Mean (SD) Median (range) Missing	2.8 (2.0) 2.3 (0.3, 8.1) 3	3.7 (2.0) 3.4 (0.8, 9.8) 13	p<0.001	

1 Relative risk figures greater than 1 indicate an advantage for FS2
2 Potential bleeding related complications ascertained by medical review of adverse events
3 RR calculated for no adverse events, due to 0 FS bleeding events
4 p value for log rank test for comparison between treatments

Kaplan Meier Survival curves were performed for time to hemostasis. The sponsor included treatment failure – censored at 10 minutes in this analysis.



Incidence of potential bleeding related complications:
Seven (10.6%) subjects in the FS2 group and 11 (15.9%) subjects in the Surgicel groups were reported to have had potential bleeding related complications. The most frequently reported complications were anemia and low hemoglobin levels. These findings are not unusual in the post operative setting to due actual blood loss and hemodilution due to fluid administration and third spacing of body fluids.

Incidence of treatment failure:

Treatment failures were defined as either:

- o Presence of bleeding at the TBS 10 minutes following randomization (defined as TTH exceeding 10 minutes) or
- o Brisk bleeding occurred requiring the need to administer additional hemostatic measures during the 10 minute observation period (defined as bleeding complications by 10 minutes)

Of the 3 FS2 and 13 Surgicel subjects listed as treatment failures 4 Surgicel treated subjects were due to brisk bleeding. The remaining ten (3 FS 2 and 9 Surgicel) were due to failure to achieve hemostasis at 10 minutes.

Safety Results

Deaths

One death occurred during the study (Subject 22008, FS2) This subject's cause of death is noted to be hepatorenal syndrome and deemed not related to study treatment. This was the only case report form submitted to the supplement.

Serious adverse events (SAEs)

Overall there were 16 SAEs reported in 12 subjects in the FS2 group (including a death) and 18 SAES reported in 15 subjects in the Surgicel group. In all of these reported cases the INVESTIGATOR did not ascribe the event due to study treatment (i.e. FS2 or Surgicel). However, the medical review team from Ethicon did ascribe a possible treatment relationship to 3 events in 3 subjects:

1 FS2 subject (#15006) who had an abdominal abscess

2 Surgicel subjects (# 15004 abdominal abscess and #26017 pelvic abscess)

Overall the most common SAEs were urinary retention, abdominal abscess and paralytic ileus.

Safety (adverse event) Summary table #7

Variable	FS2 N=67	Surgicel N=68
Total number of Adverse events	183	200

Number of patients with at least one in the following Categories:		
Adverse event	46 (68.7%)	48 (70.6%)
SAE	12 (17.9%)	15 (22.1%)
Severe adverse event	6 (9.0%)	10 (14.7%)
Adverse event requiring medical/surgical or other action	42 (62.7%)	46 (67.6%)
Related or possibly related adverse event [1]	0 (0.0%)	0 (0.0%)

1 as determined by investigators

In the pediatric group most adverse events (AEs) were seen in the Surgicel group (27 events affecting 6 of 7 subjects (85.7%)). Of the 6 Surgicel treated subjects with an adverse event, one experienced a potential bleeding complication. In the FS 2 group 2 events affected 1 of 4 (25%) subjects. In the FS2 group there were no serious or severe events.

In the adult group there were 111 adverse events affecting 26 of 39 patients (66.7%) in the Surgicel group and 88 events affecting 21 of 33 subjects (63.6%) in the FS2 group.

In the adult (age > 65 years) there were 62 events affecting 16/22 (72.7%) of subjects compared with 93 events affecting 24/30 (80.0 %) subjects.

Overall, there were no major differences in the adverse event profile for the adult population when comparing FS2 and Surgicel. In the pediatric population the numbers are low, but the Surgicel group tended to have more adverse events.

Regarding the Pediatric Assessment

The safety and efficacy of EVICEL was studied in pivotal studies covering a broad spectrum of surgical settings: liver surgery (Q-LIV-008-UK), vascular surgery (400-05-001) and in soft tissue bleeding during intra-abdominal surgery and retroperitoneal surgery. In addition supportive studies in liver surgery, vascular surgery and orthopedic surgery have been submitted to FDA.

Note that there were limited pediatric data submitted in support of the approval for use in liver surgery, as stated in the approved labeling:
“Of the 155 patients treated in adequate and well controlled studies of EVICEL Fibrin Sealant (Human) in liver surgery, eight were pediatric patients. Of these, five were less than 2 years old and three were between 2 and 12 years old. An additional l92 patients under the age of 18 have received EVICEL Fibrin Sealant (Human) during liver surgery in the UK. Use of EVICEL Fibrin Sealant (Human) in pediatric patients is supported by these data and by extrapolation of findings for safety and efficacy in adults.”

Vascular Surgery
It was not considered to be feasible to include pediatric patients since vascular grafting procedures and vascular procedures for renal dialysis using grafts are uncommon in pediatric patients.

Soft tissue bleeding in retroperitoneal or intra abdominal surgery.

Proposed Labeling:

Evicel labeling review will be done in conjunction with APLB. Final memo from APLB has not been received yet, but when it is received it will be forwarded and appended to this memo. EVICEL already carries an indication for liver surgery.
Paul Aebersold reviewed supplement 74 which contained the vascular surgeries. His memo is appended below **(APPENDIX 2)**

Conclusions:
The study met its primary endpoint; FS2 is non-inferior to Surgical for time to hemostasis at 10 minutes. There do not appear to be safety concerns for the FS2 product. Approval is recommended.

APPENDIX 1 Statistical Review Memo (Dr. Jean Wang)

STATISTICAL REVIEW AND EVALUATION

Date Populated: July 26, 2007
Type/Application ID/Amendment #: BLA 125010/105
Proposed Use (Indication): Adjunct to adjunct to hemostasis
Sponsor: Omrix.
Product name: EVICEL fibrin sealant (Human)
From: Chinying Wang, Ph. D. (HFM-219)
Through: Ghanshyam Gupta, Ph. D.
To: Debbie Cordaro (HFM-380)
Cc: Ghanshyam Gupta, Ph. D., Henry Hsu, Ph. D.,
Chron. File (HFM -215)

The study protocol entitled "A Prospective, Randomized Controlled Study to Compare the Effects of a Fibrin Sealant (FS2) as an adjunct to hemostasis for soft tissue bleeding during retroperitoneal or intra-abdominal surgery" is a phase III study comparing FS2 to Surgicel. This efficacy supplement contains study reports in support of a proposed new indication for adjunct to hemostasis in patients undergoing non-emergent retroperitoneal or intra-abdominal surgery procedures where a topical hemostat is indicated.

Statistical Review

In this mid-cycle review, the efficacy analysis for the primary endpoint has been reviewed. Efficacy was defined as FS2 was non-inferior to surgical. The primary efficacy endpoint is defined as an absence of bleeding and no treatment with any hemostatic measures (other than the assigned hemostatic adjunct, FS2 or Surgicel) at 10 minutes following randomization to treatment.

The analysis of primary endpoint is confirmed. In addition, analyses of secondary endpoints for absence of bleeding at 4 and 7 minutes following randomization have been performed. The survival analysis, using Kaplan-Meier curves was performed for time to hemostasis. The survival curves for FS2 and Surgicel are slightly different from that presented by the sponsor because the sponsor considered treatment failure as censored at 10minutes. The analyses are attached in the Appendix.

APPENDIX

(Ia) Contingency Analysis of SUCDC By TREATN (ITT primary endpoint)

TREATN By SUCDC

Count Total % Col % Row %	No	Yes	

FS2	3	63	66
	2.22	46.67	48.89
	18.75	52.94	
	4.55	95.45	

Surgicel	13 9.63 81.25 18.84	56 41.48 47.06 81.16	69 51.11
	16 11.85	119 88.15	135

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	7.084	0.0078
Pearson	6.598	0.0102

Fisher's Exact Test	Prob	Alternative Hypothesis
Left	0.0093	Prob(SUCDC=Yes) is greater for TREATN=FS2 than Surgicel
Right	0.9984	Prob(SUCDC=Yes) is greater for TREATN=Surgicel than FS2
2-Tail	0.0148	Prob(SUCDC=Yes) is different across TREATN

(Ib) Contingency Analysis of SUCDC By TREATN

TREATN By SUCDC

Count Total % Col % Row %	No	Yes	
FS2	3 2.36 18.75 4.84	59 46.46 53.15 95.16	62 48.82
Surgicel	13 10.24 81.25 20.00	52 40.94 46.85 80.00	65 51.18
	16 12.60	111 87.40	127

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	7.109	0.0077
Pearson	6.624	0.0101

Fisher's Exact Test	Prob	Alternative Hypothesis

Left	0.0092	Prob(SUCDC=Yes) is greater for TREATN=FS2 than Surgicel
Right	0.9984	Prob(SUCDC=Yes) is greater for TREATN=Surgicel than FS2
2-Tail	0.0144	Prob(SUCDC=Yes) is different across TREATN

(II) Contingency Analysis of HAE4DC By TREATN

TREATN By HAE4DC

Count Total % Col % Row %	No	Yes	
FS2	16 11.85 33.33 24.24	50 37.04 57.47 75.76	66 48.89
Surgicel	32 23.70 66.67 46.38	37 27.41 42.53 53.62	69 51.11
	48 35.56	87 64.44	135

Test	ChiSquare	Prob>ChiSq
Likelihood Ratio	7.320	0.0068
Pearson	7.213	0.0072

Fisher's Exact Test	Prob	Alternative Hypothesis
Left	0.0059	Prob(HAE4DC=Yes) is greater for TREATN=FS2 than Surgicel
Right	0.9981	Prob(HAE4DC=Yes) is greater for TREATN=Surgicel than FS2
2-Tail	0.0114	Prob(HAE4DC=Yes) is different across TREATN

(III) Contingency Analysis of HAE7DC By TREATN

TREATN By HAE7DC

Count Total % Col % Row %	No	Yes	
FS2	6 4.44 27.27 9.09	60 44.44 53.10 90.91	66 48.89
Surgicel	16 11.85 72.73 23.19	53 39.26 46.90 76.81	69 51.11

	22 16.30	113 83.70	135

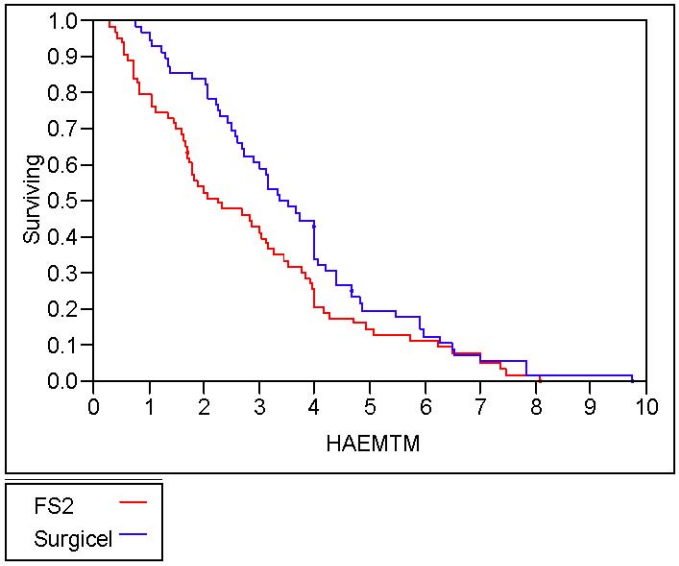
Test	ChiSquare	Prob>ChiSq

Likelihood Ratio	5.084	0.0242
Pearson	4.915	0.0266

Fisher's Exact Test	Prob	Alternative Hypothesis
Left	0.0226	Prob(HAE7DC=Yes) is greater for TREATN=FS2 than Surgicel
Right	0.9937	Prob(HAE7DC=Yes) is greater for TREATN=Surgicel than FS2
2-Tail	0.0354	Prob(HAE7DC=Yes) is different across TREATN

(IV) Product-Limit Survival Fit

Survival Plot



Time to event: HAEMTM Grouped by TREATN

Summary

Group	N Failed	N Censored	Mean	Std Error
FS2	63	0	2.82857	0.25678
Surgicel	56	0	3.69821	0.26141
Combined	119	0	3.23782	0.18689

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
FS2	2.25	1.7167	3.1	1.1333	4
Surgicel	3.3667	2.7167	4	2.25	4.6667
Combined	3	2.4333	3.4333	1.6667	4.2

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	3.6733	1	0.0553
Wilcoxon	7.3567	1	0.0067

APPENDIX 2: Review memo from Paul Aebersold

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: 03-APR-07

FROM: Paul Aebersold, Ph.D., Clinical Review Branch, HFM-392 SUBJECT: 125010/74 Fibrin Sealant Efficacy Supplement (Omrix)

TO: Debbie Cordaro, Division of Blood Applications, HFM-380

CC: Toby Silverman, M.D., Chief, Clinical Review Branch

Summary
EVICEL fibrin sealant is currently indicated for adjunct to hemostasis in patients undergoing liver surgery when control of bleeding by conventional surgical techniques is ineffective or impractical. This efficacy supplement contains two clinical study reports in support of a proposed new indication for adjunct to hemostasis in patients undergoing vascular surgery. The pivotal Phase 3 trial was conducted at 5 centers in the UK and 13 centers in the US. The evaluation sites were suture holes in polytetrafluorethylene (PFTE) grafts in end-to-side femoral or upper extremity arterial anastomoses. Manual compression with sponges was used in the control group (no products with an indication for adjunct to hemostasis). The study met its primary endpoint, superiority for fibrin sealant in control of bleeding at 4 minutes. The adverse event profile was typical for the patient population. None of the adverse events in the

control group were considered related to manual compression with sponges. However, since the trial was not blinded, it is not clear what to make of the possible causal relationship assigned to some similar adverse events in the fibrin sealant group. There was no overall imbalance in adverse events or serious adverse events between the two groups, although there were a few imbalances in particular adverse events when listed by MEDRA terms. The sponsor has acceptably responded to mid-cycle information requests. It is recommended that the efficacy supplement be approved. The sponsor has been requested to revise labeling to comport with the Physician Labeling Rule.

Trial Design
Title: A Prospective, Randomized Controlled Study to Compare the Effects of a Fibrin Sealant (FS2) Versus Manual Compression on Haemostatic Efficacy During Vascular Surgical Procedures Utilising Polytetrafluorethylene Graft Material on End-to-Side Femoral or Upper Extremity Vascular Access Arterial Anastomoses
Objective:
1. To evaluate efficacy as absence of bleeding at 4 minutes.
2. To evaluate bleeding at 7 and 10 minutes.
3. To evaluate blood loss at study site following clamp removal.
4. To evaluate the incidence of treatment failure.
5. To evaluate incidence of potential bleeding-related complications.
6. To evaluate adverse events up to five weeks follow-up.
Include:
1. Age > 18 years.
2. Elective primary or repeat vascular procedures with at least one end-to-side femoral or upper extremity vascular access arterial anastomosis (e.g., femoral-femoral, femoral-popliteal, femoral-tibial, ilio-femoral, aorto-bifemoral, abdominal aortic aneurysm, upper extremity vascular access for dialysis).
3. Use of polytetrafluoroethylene (PTFE) grafts and polypropylene sutures (size 5-0 or 6-0) with a 1:1 needle-to-thread ratio.
4. Following initial clamp release, surgeon's determination that adjunctive measures are needed to obtain hemostasis.
Exclude: 1. Autologous conduits or prosthetic material other than PTFE.
2. Emergency surgery.
3. Known intolerance to heparin, blood products or component of the study product.
4. Unwilling to receive blood products.
5. Autoimmune immunodeficiency diseases, including known HIV.
6. Intra-operative finding that may preclude conduct of study procedure.
7. Alcohol or drug abuse.
8. Another investigational drug or device within 30 days.
9. Pregnant or nursing.

Study: Multi-center, randomized, controlled with a total of 150 subjects at 15 sites. FS2 will be prepared for all subjects prior to randomization. Subjects will receive 70 IU/kg heparin before arterial clamping and, if applicable, heparin reversal will be documented. For procedures with more than one femoral artery anastomosis, the study site will be the last anastomosis to be completed. After suturing, the clamps will be removed and additional sutures placed as needed. After securing the suture line, if remaining bleeding indicates need for an adjunctive measure, the clamps will be reapplied, coagulation parameters and vital signs obtained, and the randomization envelope opened. Randomization is stratified by site and for femoral versus

upper extremity procedures.
For a subject randomized to fibrin sealant, the entire product (4 ml) should be dripped onto the anastomosis site. (If the entire volume is not used, the remaining volume should be recorded on the CRF and placed for destruction in biological waste.) The clamps will be removed 1 minute following the administration of fibrin sealant.

For a subject randomized to manual compression, the clamps will be released immediately and the prepared FS2 will be removed from the OR. A sponge with light manual pressure will be applied to the anastomosis site. At the landmark evaluation times, one corner of the sponge should be cautiously lifted and, if no bleeding is observed, the sponge should be carefully removed.

If any bleeding is observed during removal of the sponge, it should be replaced immediately. If brisk bleeding occurs at the study site during the up-to-10 minute observation period and requires further hemostatic measures, or if hemostasis has not been obtained by 10 minutes, the outcome will be recorded as a treatment failure. Fibrin sealant is not permitted as a further hemostatic measure for treatment failures.

Evaluation:
Hemostasis at 4, 7, and 10 minutes following randomization. Blood loss following clamp removal will be collected using dry sponges, which will be weighed. If applicable, total daily drainage, drainage characteristics, and date of drain removal. On the first day post-surgery, Hb, Hct, RBC, MCV, MCH, platelets, MPV, WBC with differential, PT, aPTT, and INR. AEs will be recorded to hospital discharge. Subjects will be evaluated at a five week (. 7 days) follow-up visit.

Analysis: The null hypothesis is that the proportion of subjects with bleeding (yes/no) at 4 minutes is the same for subjects receiving FS2 as for those receiving manual compression. With 144 subjects, the study has 90% power to detect a difference in proportions of 0.28 when the proportion in the control group is 0.35, using a two-sided Chi-square test. To account for “drop-outs”, the sample size has been increased to 150 subjects.

The “safety set” will contain subjects who receive at least one treatment; the “full analysis set” will contain all randomized subjects (ITT), and the “per protocol set” will contain subjects in the full analysis set who have no major protocol violations (determined at a pre-database lock meeting). The primary analysis of the primary endpoint will be assessed using ITT, to include a worst case sensitivity analysis if there are any missing data. Analysis of the “per protocol set” will be considered supportive. A logistic model will include treatment center and artery type.
Baseline
There were no substantial differences between groups in patient demography or medical history. There were also no substantial differences between groups in clinical laboratory parameters, hemoglobin in particular since the study pertains to control of bleeding. Efficacy
Hemostasis at suture hole sites at 4 minutes was achieved in a significantly greater proportion of subjects in the fibrin sealant group than in the control group (85.3% versus 38.9%). However, for one of the subjects in the fibrin sealant group was counted as a success at 4 minutes, yet required additional measures of hemostasis within 10 minutes; this subject should be considered a failure. There were five subjects for whom documentation was questionable for the time of clamp release. Thus a worst case efficacy analysis was done in which the two subjects in the fibrin sealant group were considered failures and the three subjects in the

control group were considered successes, and the outcome was still highly significant.

At 10 minutes, the sponsor claims that hemostasis was obtained in 72/75 subjects (96%) in the fibrin sealant group and in 50/72 subjects (69.4%) in the control group. However, the incidence of treatment failure is 8% for fibrin sealant, consisting of 4% continued bleeding at 10 minutes and 4% requirement for other hemostatic measures during the 10 minute observation period. Since the subjects in those two categories were non-overlapping, the sponsor cannot claim 96% success for fibrin sealant at 10 minutes, only 92% success. The 3 subjects who required other hemostatic measures cannot be reported as successes for fibrin sealant.

At one site (Birmingham), the investigator did not wait 10 minutes for 3 of 4 subjects in the control group before using measures of hemostasis besides manual compression. The record for this site appears to indicate failure to follow the protocol. Data from this site should therefore be excluded from the efficacy analyses.

Considering primary and secondary efficacy endpoints, fibrin sealant is an effective adjunct to hemostasis as assessed by reduction in time to hemostasis at suture hole sites where bleeding is not amenable to control by standard surgical techniques such as suture or ligature. Safety
There were somewhat more adverse events in the control group (158 in 72 subjects) than in the fibrin sealant group (113 in 75 subjects).

The percentage of subjects with serious adverse events was essentially the same in the two groups, approximately 30%. By MEDRA terms, there were a few imbalances such as 5 cases each of anemia and congestive heart failure in the control group versus none in the fibrin sealant group, and conversely 5 cases of graft thrombosis in the fibrin sealant group versus none in the control group.
With respect to graft thrombosis, there were also 2 cases of graft occlusion in the fibrin sealant group and 5 cases in the control. The sponsor points to 4 additional cases of graft thrombosis/occlusion coded as peripheral vascular disease (fibrin sealant) and AV fistula thrombosis, graft infection, and graft complication (control), bring the total to 8 in each group. More cases of graft thrombosis/occlusion in the fibrin sealant group than in the control group occurred in the first 12 days after surgery, whereas by week 5, graft thrombosis/occlusion was balanced between groups. Despite the somewhat different time course in the two groups, it would be difficult to ascribe graft thrombosis/occlusion days later to the choice of hemostat during surgery.

Four cases of graft site infection were reported in the fibrin sealant group and 5 cases in the control group. Two cases in the fibrin sealant group were considered possibly related to treatment. Since 9 adverse events overall were considered possibly related to fibrin sealant and none to manual compression, investigators may have been influenced by their knowledge of the treatment assignment. It does not appear from the number of reported cases of graft infection in the two groups that fibrin sealant increases any risk for this particular adverse event.

There were two deaths in each treatment group. The sponsor states that none of the deaths was considered to have any relationship to the study treatment, but in once case the investigator considered the death possibly related to fibrin sealant. The triggering adverse event appears to have been a Staphylococcus infection. In the sponsor’s

Discussion and Overall Conclusions, attention is drawn to more cases of anemia in the control group (9) than in the fibrin sealant group (5). Granted that there were somewhat more adverse events in the control group, nevertheless there is really no sound basis for singling out anemia. Blood transfusions in the two groups were quite balanced and there is no evidence that the reported cases of anemia had anything to do with bleeding from suture holes in the synthetic graft material, the only location where fibrin sealant could have had an effect on blood loss.

Mid-cycle Information Request

1. In several cases, it appears that hemostasis has been analyzed as successful at 4, 7, or 10 minutes despite the use of hemostatic measures in the 10 minute observation period other than the assigned treatment. We do not consider hemostasis to have been successful in these cases (25006, 29006, 30007, and 30008). Please revise your efficacy analyses with these subjects counted as failures. This request means that you will need to revise the summary tables of effectiveness since, for example, hemostasis by 10 minutes cannot be reported as 96% in the fibrin sealant group.

2. The Birmingham site stands out for its use of other measures of hemostasis within the 10 minute observation period. In 3 out of 4 cases in the manual compression group, the investigator did not wait the protocol-specified 10 minutes to assess whether the study treatment could achieve hemostasis on its own. Therefore, we request that you conduct efficacy sensitivity analyses that:

- exclude data from the Birmingham site; and
- consider the Birmingham control group cases to be successful at 10 minutes.

3. It is not apparent from its text that the study report includes the protocol-specified analysis of blood loss at the study sites. Please either:

- specify the locations of this analysis and of the data in the line listings; or
- submit the analysis and the data.

4. With respect to the analysis of graft thrombosis/occlusion, you note in a footnote to Text Table 11 that you have included cases that were reported as peripheral vascular disease, graft infection, and graft complication. Please identify the subjects and explain on what basis these other adverse events are considered to be graft thrombosis/occlusion.

5. Please present the cases of graft thrombosis/occlusion for each study group in graphical form according to time after surgery. Not yet having an explanation for the cases referred to above, we request that this presentation be done with and without those cases. It appears that some cases of graft thrombosis/occlusion in the fibrin sealant group occurred earlier than in the manual compression group. If your analysis shows such earlier occurrences, please discuss the implications of this finding.

6. There were two deaths in each treatment group. In Section 12.2.3, ANALYSIS OF ADVERSE EVENTS, you state that none of the deaths was considered to have any relationship to the study treatment. This statement does not acknowledge the investigator's consideration that patient 20010's infection and subsequent death was possibly related to the fibrin sealant treatment. Please explain why you do not agree with the investigator's assessment of possible relationship.

7. Please present and discuss an analysis by treatment group of the number of subjects

who had to return to surgery. This analysis should include: • any cause to return to surgery; and • return to surgery specifically for a graft site complication.

Response to Information Request

The sponsor responded appropriately to request 1, but did not apply that request to the further analyses of request 2. Treatment failures, as defined by the need for additional hemostatic measures within 10 minutes, need to be considered treatment failures in the analysis excluding site 3 and the analysis considering site 3 controls as successes. This will make a small difference in the percentage of successes, but will not alter the primary statistical outcome of the study.

Blood loss at the study site, originally a secondary endpoint, was dropped in a protocol amendment after discussion with investigators.

With respect to graft thrombosis/occlusion, the following cases were included:
1. Worsening of peripheral vascular disease (fibrin sealant);
2. Infected graft (manual compression);
3. Clotted AV fistula (manual compression); and
4. Graft complication (90% stenosis) (manual compression).

The response does not explain why a graft infection should be considered to be a case of thrombosis/occlusion.

With respect to timing of graft thrombosis/occlusion, in the first week there were 5 cases in the fibrin sealant group and 3 in the manual compression group. In one shunt case in the fibrin sealant group, the subject was returned to surgery. The venous anastomosis was opened, but no thrombus was found. Thus this case can reasonably be considered not to reflect thrombosis/occlusion. In any even, 5 versus 3 or alternatively 4 versus 3 cases in the first week do not raise much concern. The other cases in the fibrin sealant group occurred on days 12, 16, and 21, whereas the other cases in the manual compression group occurred on days 19, 32. 41. and 46. Taking all these cases into account, there is an impression of earlier occurrence in the fibrin sealant group, but it is difficult to relate thrombosis/occlusion that occurred days later to the choice of hemostat during surgery.

With respect to return to surgery, there were no differences between test and control groups, either for any surgical intervention or specifically for graft site complications. Final Information Request The sponsor should be requested to analyze the efficacy data considering both requests 1 and 2 together. For purposes of the package insert and any promotional materials, data from site 3 should simply be excluded (as opposed to imputing the cases in the control group to be successes). The labeling, submitted in July 2006, must be revised to comport with the Physician Labeling Rule, which took effect in June 2006.

Recommendation

The final information requests have been satisfied (after several iterations of the labeling in the new format). The data support fibrin sealant to be a safe and effective adjunct to hemostasis in vascular surgery, and the new indication is recommended for approval.