

MEMORANDUM



Department of Health and Human Services
Public Health Service
United States Food and Drug Administration
Center for Biologics Evaluation and Research



To: File (STN 125392/0 Original BLA Evarrest™)

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For: Filing of Midcycle for Original BLA STN 125392/0- Omrix’s Fibrin Pad Evarrest™

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This memorandum is a summary of the pre-clinical program based on the preliminary non-clinical review of the original biological license application (BLA) for Evarrest™, Fibrin Sealant Pad. Evarrest is indicated as adjunct to hemostasis for mild to moderate bleeding for soft tissue during retroperitoneal, intra-abdominal, pelvic and (non-cardiac) thoracic surgery when standard surgical methods of hemostasis are ineffective or impractical. There were pre-clinical deficiencies identified in STN 125392 BLA for Omrix’s Fibrin pad, Evarrest™, based on review of the pharmacological and toxicological data presented. The Sponsor has responded to the deficiency information requests sent in reference to safety concerns (fibrin pad complete absorption) to be addressed for completion of file at the time of mid-cycle filing.

I. Letter Ready Comments

Based on the review of pharmacological and toxicological data presented by the sponsor, the following information is requested:

There appears to be an outstanding safety concern related to the long-term presence of the product (due to its slow degradation) particularly in malignant patients related to potential carcinogenesis. It is noted that EVARREST can remain in situ $\geq 60+$ days following inflammation and possibly adhesion and thrombotic events post-surgery. Therefore, we recommend the sponsor perform a well-powered and controlled study to determine the carcinogenicity potential as well as the mechanism of cancer development in an animal model

following use of EVARREST. For further guidance please refer to ISO 10993, ICH S1A, ICH S1B and ICH S1C(R2), which can be found at <http://www.fda.gov/cder/Guidance/5544fnl.htm>

II. Background

Omrix has manufactured a Fibrin pad that consists of a sterile bio-absorbable fibrin patch and ---(b)(4)---, which is currently used as an adjunct to hemostasis consisting of a cellulose matrix and biological coating. ---(b)(4)---, contains of a two component coating, human thrombin and fibrinogen ((b)(4)), is viral inactivated by pasteurization, licensed under ---(b)(4)---. The Fibrin pad is composed of ---(b)(4)--- human fibrinogen and human thrombin and an oxidized regenerated cellulose (ORC) backing and polyglactin 910 of 4 in. x 4 in. (10.2 cm x 10.2 cm) pad size. -----(b)(4)-----
----- review of 4”X4” (standard) pad ---(b)(4)----. This fibrin pad was reviewed under IND 13563 fibrin pad for indication as an adjunct to hemostasis for mild to moderate bleeding for soft tissue during retroperitoneal, intra-abdominal, pelvic and (non-cardiac) thoracic surgery when standard surgical methods of hemostasis are ineffective or impractical. Additionally, under current review in IND -----
----- (b)(4)-----
----- . The Sponsor claims that there is currently a need for an alternative method for the safe and effective treatment of soft tissue bleeding when the use of traditional methods is ineffective or impractical.

III. Proposed Use and Doses

The amount of EVARREST required is determined by the area being treated and the method of application. In this instance, 4”X4” pads (standard) will be applied to target surgical site. The treating physician prescribes the final dose. The sponsor defined indication as an adjunct to control soft tissue bleeding during abdominal, retroperitoneal, pelvic, and (non-cardiac) thoracic surgery with note to contraindications of brisk or severe bleeding or as primary hemostatic agent. The maximal number of pads tested has been allocated to four standard pads in a single surgical site in clinical trials.

IV. Internal FDA Position Statement Related to Carcinogenicity with Fibrin Pads

With the use of combination devices and biologic products increasing, it is necessary to address potential safety concerns related to use of these products. To date, off-label use of these products has occurred; however, the safety and effectiveness of these products has not been adequately accessed in off-label use. Specifically, the use of Fibrin pads and/or similar products is presenting more regulatory challenges that will have to be evaluated due to the complexity of the starting products and the more complex resulting final product. Fibrin pads consist of a device coated by with a biologic (i.e. thrombin alone and/or fibrinogen), usually a fibrin sealant, manufactured as a single unit with biological and mechanical properties. The use of fibrin pads had shown an increased risk of multiple organ adhesions, increased inflammation, and possible hemorrhage (re-bleeding) at treatment site. Studies also suggest that lung and kidney embolization can occur after device implantation (greater risks when major blood vessels are involved). At this time there is only one licensed fibrin patch in OBRR, TachoSil, which is composed of equine collagen patch coated by human fibrin sealant (STN 125352). To date, there have been little to no carcinogenicity studies or clinical monitoring related to fibrin pads and similar products. Furthermore, clinical reporting is likely obtained from passive reports making it difficult to assess carcinogenicity signals in patients accurately. Carcinogenicity is of particular concern when using fibrin pads due to the large portion of thoracic/abdominal surgeries and the robustness of

malignant patient population subjected to product use following surgeries. Fibrin pads appear to have substantially longer presence (or bioavailability) compared to pads or biologic(s) alone. Since cancer patients are particularly pre-disposed to malignancy, it is imperative that the carcinogenic potential of these products is assessed. Current literature indicates that patients treated for malignancy are pre-disposed to greater risks of recurrence; and are at even greater risks when exposed to chronic inflammation, autoimmune diseases, and infection for malignancy recurrence. There is uncertainty whether there is a mechanistic link between inflammation and carcinogenicity; although signal transduction pathways do intersect between these processes (cytokines release and NFκB), particularly malignancy activation; and potential links are beginning to emerge in research. In addition, there is growing evidence to substantiate a connection between inflammation and tumor development to promote tumorigenesis, thus malignancy. For the assurance of patient population and due diligence in addressing safety concerns related to product use, carcinogenesis should be addressed. Taken together, a statement should be conveyed to sponsors seeking approval and licensure of Fibrin pads or similar products regulated by OBRR to address carcinogenicity until further notice or findings.

1. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet*. 2007;369:1603-1613.
2. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med*. 2007;356:2131-2142.
3. Mantovani A. Cancer: inflammation by remote control. *Nature*. 2005;435:752-753.
4. Baniyash M. Chronic inflammation, immunosuppression and cancer: new insights and outlook. *Semin Cancer Biol*. 2006;16:80-88.

V. Responses and Comments to Non-clinical Information Requests

The following information requests for non-clinical deficiencies were sent to the sponsor:

Non-Clinical

1) To facilitate our review of pre-clinical studies, please specify those that directly address the indication proposed in the BLA and provide a reviewer's guide in the form of a table that indicates for each submitted study report:

- a. Study purpose (aspect of claimed clinical indication supported by the study).**
- b. Study date.**
- c. GLP/non-GLP.**
- d. Fibrin Pad batch number.**
- e. Site and date of manufacture.**
- f. Concentration of fibrinogen and thrombin components.**
- g. Other information pertinent to characteristics / manufacture of Fibrin Pad investigated in the particular study, e.g., sterilization method**

FDA Reviewer Response/Comment(s): The Sponsor concurred.

2) It is noted that there are differences for the final endpoint (day) on complete absorption of the Fibrin Pad in pre-clinical reports ranging from 56 days up to 119 days (Study Reports 05-0636,06-0658,08-0146 and 08-0220); and these variations extend to animal models (nude mice, rats, and swine) tested. You state that the complete absorption/degradation is 56 days for clinical trial observation period. Please submit the actual number of days for complete absorption of EVARREST under "normal" conditions and "worst-case scenario" conditions as determined in pre-clinical studies or based on clinical experience (clinical observations) following EVARREST use (final clinical grade product). Please provide an explanation for differences noted in absorption rates in animals

tested; and note identifiers for the product tested in each study (batch number, production site, Fibrin Pad composition). Additionally, please provide justification to establish 56 days as an accurate endpoint estimate for complete Fibrin Pad absorption in clinical trials.

FDA Reviewer Response/Comment(s): The sponsor has attempted to address concerns related to complete absorption of the fibrin pad and discrepancies in data submitted. It appears that in immunocompromised (immunodeficient) conditions, the absorption of fibrin pad may be prolonged. This is of note since a large portion of patients are cancer patients and/or patients with pre-existing conditions resulting in surgery. This alert an additional safety concern related to potential of carcinogenesis from the slow degradation of fibrin pads (see Statement Related to Carcinogenicity with Fibrin Pads).

VI. Summary of Relevant Non-Clinical Studies in STN 125392/0

Non-clinical studies were complete with various lots of fibrin pad and a large portion of studies were for biocomparability since the product has had (b)(4) manufacturers (in (b)(4) facilities) since the submission of initial IND 13563. All of the absorption pre-clinical studies were complete on earlier versions of the fibrin pad (2008 or prior). The fibrin pad lots tested in pre-clinical studies were not used in clinical trials. The Chemistry, Manufacturing and Controls (CMC) reviewer has concurred that the fibrin pad products are biocomparable for analysis and use in clinical trials in final drug product phase. Previous studies also indicated that there were notable adverse events associated with product use including pulmonary embolism formation (uncertain causes), re-bleeding, hemorrhage at wound site, and adhesions. It appears that the immune mediated responses following treatment with fibrin pad, EVARREST, is increased in normal animals vs. immunocompromised animals (increased giant cells, inflammation & inflammatory responses, fibrosis, etc.).

Abbreviations

FIB= fibrinogen Gr. = groups d= day(s) timepts.= timepoints hr = hour(s) THR=thrombin

FP=fibrin pad final product diff.= differences s.s.= statistically significant

*Study 05-0636: Studied absorption in rat for matrix only (non-embossed) & it was essentially absorbed in 56 d in rat (subcutaneous)

Study Number	Type of Study	Synopsis of Study	Dosage, Batch	Results	Comments
06-0658	Proof-of- concept Efficacy Absorption (immunocompetent)	Partial nephrectomy in Swine for 14 d or 56 d	----- (b)(4) ----- -----	FP appears effective, Absorption =5/6 animals <10% FP remnants	AEs occurred; Fibrin pad was used as primary management-not adjunct in study (contraindication for FP use)
09-0074	Biocomparability Proof-of Concept	Partial nephrectomy in Swine w/ (2 lots) embossed vs. non-embossed pad for 48 hr	----- (b)(4) ----- -----	Embossing did not make s.s. difference in study results for test gr.	There were no changes noted in FP effectiveness
10-0143	Biocomparability	High dose optimization for FP Partial nephrectomy in Swine w/ (2 lots) for 48 hr	----- (b)(4) ----- --	The final dosing was optimized to current formulation since these doses were too high for biologics	There were no changes noted in FP effectiveness
09-0188	Biocomparability	Low dose optimization for FP Partial nephrectomy in Swine w/ (2 lots) for 48 hr	----- (b)(4) -----	The final dosing was optimized to current formulation & this dose was not selected	There were no s.s. changes noted in FP effectiveness

09-0274	Proof-of-concept	Exaggerated Coagulopathy model using partial nephrectomy in swine for 48 hr	------(b)(4)-----	FP appears effective	AEs occurred
69718	FP Implantation Proof-of-concept Efficacy	Liver lobectomy and partial splenectomy in rabbit for 7 and 14 d observations	------(b)(4)-----	FP appears effective	FP showed ingrowth by d 14; absorption had not occurred at end of study
05-0474	Absorption	Subcutaneous implantation in Rat for 90 d	------(b)(4)-----	FP was absorbed by 90 d; no other timepts were observed	Granulomas remained in wound site when FP was absorbed up to d 90
08-0122 08-0146 (08-0220)	Absorption	Intrahepatic and Intramuscular implantation in athymic Rat for 56 d	------(b)(4)-----	FP was absorbed by 90 d; no other timepts. were observed	There were severity levels diff. between gr.'s healing & effects
09-0077	Absorption	Intrahepatic implantation in athymic vs. normal Rat for 28 d	------(b)(4)-----	At 28 d, ingrowth tissue was normal < athymic rats treated w/ FP	Absorption was not complete in either rat model at 28 d

