

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

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This memorandum is a summary of the non-clinical program based on the pharmacological/toxicological review of the original biological license application (BLA) for Evarrest™, Fibrin 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 carcinogenicity potential and sequential multiple use of product) to be addressed for completion of file review. The safety concerns are not completely concurred by FDA; and remain outstanding.

I. Recommendation

I will defer the final decision to licensing status for STN 125392 Original Biological Licensure Application (BLA) for Omrix’s Fibrin Pad, EVARREST, to the clinical review branch (CRB) since there is clinical experience using the product. There are notable safety concerns related to product use in proposed indication for adjunct to hemostasis based on pre-clinical studies including adhesion formation, re-bleeding, thrombotic events, and inflammation; the same safety concerns which were noted in clinical trials. The use of clinical data will be used in lieu of additional pre-clinical data to substantiate the safety profile of the fibrin pad.

II. Letter Ready Comments

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

1. Please submit either pre-clinical or clinical data that support subsequent repeated use of Fibrin pad. There additional safety concerns with subsequent and/or sequential operations resulting in multiple use/chronic use of product that needs to be addressed in a repeat dose toxicity animal study. The study should entail a recovery period, histopathology, hematology and serum chemistry panel, etc. in parallel with ADME (specifically complete absorption) determination in a pre-clinical model as related to *in situ* administration of the (final) fibrin pad in repeat use setting (worst case clinical scenario). Clinical repeat use (experience) data can be submitted in lieu of additional pre-clinical studies to address these safety concerns.

III. Background

Omrix has manufactured a Fibrin pad that consists of a sterile bio-absorbable fibrin patch and

----- (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)-----

----- requesting 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, 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.

IV. 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.

V. Internal Comments

There appears to be a safety concern related to the long-term presence of the product (due to its slow degradation) 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 determine the carcinogenicity potential of fibrin pad. This can be addressed by completing longer-term ($> 60+$ days) clinical monitoring and

follow-up in clinical trials, ex vivo cell studies and/or the sponsor performing a well-powered and controlled study to 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>

The sponsor has submitted a literature search on the carcinogenic potential of PG910, and cited literature and guidance to obviate the need for carcinogenicity studies in animals for complete fibrin pad. This literature search was in response to an information request during the BLA review.

The sponsor's responses was not concurred; and further disputed by FDA/CDRH review and precedence with similar products.

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 assessed 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.

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. The indication of adjunct to hemostasis was tested in previous pre-clinical studies which indicated that there were notable adverse events associated with intended product use including pulmonary embolism formation (uncertain causes), re-bleeding at treatment bleeding site, inflammation (persistent), hemorrhage at wound site, and adhesion formation at treatment bleeding site. 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.). Only the pre-clinical studies using fibrin pad in current proposed indication (adjunct) were summarized below to support the characterization of the product. The safety profile for fibrin pad cannot definitively be established based on pre-clinical data.

General Comments for Non-clinical Data: To date, acute dose toxicity (10X pads use simultaneously), local tolerance, degradation, mutagenicity, immunogenicity and efficacy (proof-of-concept) studies in the pre-clinical program have been submitted for Omrix's Fibrin Pad, EVARREST. Adverse events following proposed use for fibrin pad have been noted. There are clinical data submitted in lieu of additional non-clinical studies to attempt to address safety concerns related to current indication to support clinical market use of EVARREST fibrin pad. Previous clinical experience that has been compiled on EVARREST negates the necessity for additional pre-clinical toxicity studies in additional higher order animals as component of pre-clinical program at this time in current indication for efficacy. However, the sponsor will have to address outstanding safety concerns related to product use including sequential multiple use of fibrin pad. Immunogenicity has been monitored in pre-clinical studies and clinical trials; however it continues to be a major concern for product use--thus clinical monitoring will continue to expand database.

05-0474	Absorption	Subcutaneous implantation in Rat for 90 d	------(b)(4)-----	FP (at 10X conc.) was absorbed by 90 d; no other timepts were observed	Fibrosis & Granulomas inflammation 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; inflammation
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

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

Abbreviations

FIB = fibrinogen Gr. = groups d = day(s) timepts.= timepoints hr = hour(s) THR = thrombin diff.= differences
 FP = fibrin pad final product s.s.= statistically significant AEs = Adverse events
 TEs =Thrombotic events PEs = pulmonary embolisms Conc. = concentration