

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™)
From: La’Nissa A. Brown, Ph.D., Pharmacologist, Division of Hematology (DH)/OBRR
Through: Yolanda R. Branch, Ph.D. for Anne M. Pilaro, Ph.D., Supervisory Pharmacologist, DH/OBRR
For: Filing of Midcycle for Clinical Hold Response for BLA STN 125392/0-Omrix’s Fibrin Pad, Evarrest™

This memorandum is a summary of the pre-clinical program based on the previous non-clinical review of the original biological license application (BLA) for Evarrest™, Fibrin Sealant Pad. There were no new non-clinical data submitted for review in the clinical hold response. The pre-clinical studies has previously been reviewed in STN 125392/0 Original BLA Evarrest™.

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. 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. ----- review of 4”X4” (standard) pad at this time. 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 Applicant 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. The maximal number of pads tested has been allocated to four standard pads in a single surgical site in clinical trials.

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 (non-clinical and clinical) 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	------(b)(4)-----	FP appears effective	AEs occurred

		in swine for 48 hr			
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

