

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 BLA EVARREST™ SBRA & Label)

From: La’Nissa A. Brown, Ph.D., Pharmacologist, Division of Hematology (DH)/Office of Blood Research and Review (OBRR)

Through: Anne M. Pilaro, Ph.D., Supervisory Toxicologist, DH/OBRR

For: Original Biological License Application (BLA) STN 125392/0- Omrix’s EVARREST, Fibrin Sealant Patch, Non-clinical Labeling for Package Insert (PI) and Summary Basis for Regulatory Action (SBRA)

This memorandum contains the final non-clinical label for the package insert (PI) and the summary basis for regulatory action (SBRA) for EVARREST™ Fibrin sealant patch based on review of the pharmacology and toxicology information in the application STN BLA 125392/0.

EVARREST Non-clinical Label

NONCLINICAL TOXICOLOGY

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with EVARREST. There are no adequate and well-controlled studies in pregnant women. It is also not known whether EVARREST can cause fetal harm when administered to pregnant women or can affect reproductive capacity. EVARREST should be given to a pregnant woman only when no other options exist.

12.3 Pharmacokinetics

Human pharmacokinetic studies have not been performed. Because EVARREST is only applied topically, systemic exposure or distribution to other organs or tissues is not expected. Animal studies with topically applied EVARREST showed incomplete resorption of the patch at 8 weeks after application. [*Animal Toxicology*, 13.2]

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of EVARREST, or studies to determine the effects of EVARREST on genotoxicity or fertility have not been performed. An assessment of the carcinogenic potential of EVARREST was complete to demonstrate minimal carcinogenic risk from product use.

13.2 Animal Toxicology and Pharmacology

In swine and rodent models, topically applied EVARREST was incompletely resorbed at approximately 8 weeks after application. Remnants of EVARREST™ (~5% of initial patch) remained in the rodent and swine models, degrading exponentially over time. The biological components of EVARREST are degraded by fibrinolysis and phagocytosis, similarly to endogenous fibrin. As absorption of EVARREST progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated.

Official Summary Basis for Regulatory Action (SBRA)

4. Non-clinical Pharmacology/Toxicology

General Review Conclusions

The Applicant (Omrix) has completed an extensive non-clinical program to demonstrate the safety and effectiveness of EVARREST™. Based on these findings and in addition to human experience in clinical trials, EVARREST™ is not expected to pose any greater safety risks than the similar products that are currently marketed. Long-term animal studies to evaluate the carcinogenic potential of EVARREST™, or studies to determine the genotoxicity or the effect of EVARREST on fertility have not been performed.

Pharmacological/Toxicological Findings

EVARREST™ was determined to be safe for its intended use as an adjunctive hemostat, based on non-clinical studies (Good Laboratory Practices [GLP] and non-GLP compliant) and its clinical use in surgical settings both within and outside of the United States. The pre-clinical program consisted of a series of studies to demonstrate the safety and effectiveness of EVARREST™. Completed non-clinical studies included safety pharmacology (rats), efficacy (rats, minipigs, and beagles), local tolerance (rabbits, minipigs, and dogs), antigenicity (guinea pigs, rats, and minipigs), mutagenicity, degradation, immunogenicity (guinea pigs), and acute toxicity studies (minipigs and dogs). The indication of adjunct to hemostasis was tested in pivotal non-clinical studies which demonstrated that there were notable adverse events associated with intended product use including thromboembolic events, re-bleeding at treatment bleeding site, inflammation (persistent), hemorrhage at wound site, and adhesion formation at treatment bleeding site. These adverse events were predictive for human use of product as confirmed by adverse events in clinical trials. The Applicant has completed a carcinogenic risk assessment analysis, and limited studies to address potential long-term adverse effects from product use. The limited assessment data indicated that the carcinogenic potential of the product should be minimal and comparative to similar

products currently marketed. However, long-term clinical monitoring for carcinogenicity will continue as a post-marketing commitment for the pharmacovigilance plan to address this concern because similar products have demonstrated that carcinogenicity is a concern in the general patient population.

EVARREST™ was acutely tested in animals at up to 10 times the intended clinical dose (~1 standard size pads/surgery; 10 pads tested) in a single procedure, for up to two weeks without any adverse events reported. Pharmacokinetic studies demonstrate that degradation of the fibrin sealant component of EVARREST™ begins within hours, as the fibrin is metabolized by fibrinolysis and phagocytosis. However, small remnants of EVARREST™ may be present up to 8 weeks after application (~5% of patch remaining in animal studies), with remnants degrading exponentially. There is a safety concern regarding immunogenic responses from foreign components of EVARREST™ being introduced to patients following administration, until complete degradation of EVARREST™ occurs. Therefore, immunogenicity and complete resorption of EVARREST™ will be clinical monitoring points as post-marketing commitments in both acute and long-term surgical settings. In limited non-clinical studies, EVARREST™ does not appear to be antigenic and will not likely result in anaphylaxis. The safety profile determined for EVARREST™ is sufficient to support approval of the Biological License Application (BLA). Previous experience with similar products indicates potential for post-operative re-bleeding, neutralizing antibody formation following administration, and minimally likely, thromboembolic events.

The Pharmacology/Toxicology Reviewer, La’Nissa A. Brown, recommends Biological License Application (BLA) approval.