

MEMORANDUM



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



To: Administrative file of BLA STN 125392/0

Meeting Date: 7 September 2012

From: Natalya Ananyeva, PhD, Senior Staff Fellow, Laboratory of Hemostasis, Division of Hematology, OBRR
Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch, Division of Hematology, OBRR

Product: Fibrin Sealant Patch [EVARREST]

Applicant: ETHICON, Inc.

Subject: Discussion of the safety aspect of the ORC component of EVARREST

Meeting Attendees:

Jay Epstein, MD, Director, Office of Blood Research and Review (OBRR)
Ginette Michaud, MD, Deputy Director, OBRR
Mark Weinstein, MD, Associate Deputy Director, OBRR
Basil Golding, MD, Head, Division of Hematology (DH), OBRR
Nisha Jain, MD, Chief, Clinical Review Branch, DH, OBRR
Tim Lee, PhD, Chief, Laboratory of Hemostasis, DH, OBRR
Kimberly Lindsey, MD, Clinical reviewer of the BLA for EVARREST
Natalya Ananyeva, PhD, Product reviewer of the BLA, Chairperson

Meeting Objective:

To update the OBRR upper management on the discussions with the CDRH regarding the safety aspect of the oxidized regenerated cellulose (ORC) component of EVARREST, and to seek advice on adequate reflection of this aspect in the Prescribing Information for EVARREST.

Meeting Minutes:

The combination fibrin sealant product under review, EVARREST, contains a device component - the backing layer composed of polyglactin 910 (PG910) non-woven fibers and an oxidized regenerated cellulose (ORC) supporting layer.

A consultative review with CDRH regarding the device component of EVARREST raised the following concerns about the ORC component of EVARREST (an email correspondence from Dr. Elaine Blyskun, Chief, Ob Gyn Devices Branch, Division of Reproductive, Gastro-Renal and Urological Devices, dated August 30, 2012):

- The oxidized regenerated cellulose (ORC) component in EVARREST ---b(4)-----
----- The ---b(4)-----
----- Prescribing Information repeatedly states that -----b(4)-----

- CDRH wants CBER to understand that in the presence of blood -b(4)-----

Dr. Lindsey provided background information on the product and an overview of the regulatory history for the BLA, STN 125392/0. Dr. Ananyeva explained the structure and mechanism of action of EVARREST (please refer to the attached Power Point presentation for illustrations).

Regulatory History:

This submission is a Biologics License Application (BLA) from Ethicon, Inc. for EVARREST Fibrin Sealant Patch, a sterile, bio-absorbable combination product.

The original BLA was submitted on November 19, 2010. Ethicon has conducted several clinical trials to support the efficacy and safety of EVARREST. The soft tissue surgery study conducted under IND 13563 served as the “licensing” study for the original BLA submission.

Approximately 3 months prior to the PDUFA goal date of September 19, 2011, Ethicon submitted the final study report for a Phase 3 soft tissue surgery study conducted outside the US. This report was intended to provide additional supportive safety information for the BLA.

Although EVARREST was demonstrated to be effective as an adjunct to hemostasis in both the US soft tissue surgery study conducted under IND 13563 and the soft tissue surgery study conducted outside the US, following a complete review of the submission, FDA issued a Complete Response (CR) letter on September 19, 2011. One key reason cited for the issuance of the CR letter included insufficient clinical information to assure safety of EVARREST in the intended surgical population. Specifically, the submitted data showed an unfavorable trend against EVARREST with regard to thrombotic events (TEs). The additional soft tissue surgery study did not provide sufficient safety information to recommend approval.

FDA requested additional safety data from a study designed with a prospective monitoring plan for thrombotic events to assess the safety of EVARREST. In their response to the CR letter dated 30 March 2012, Ethicon submitted a report for an additional hepatic resection surgery study conducted outside the US. The total safety database for EVARREST used as an adjunct to hemostasis consists of 239 subjects. PDUFA Action Due Date is 29 September 2012.

Indication:

EVARREST is indicated as an adjunct to hemostasis with manual compression for soft tissue bleeding during open retroperitoneal, intra-abdominal, pelvic, and non-cardiac thoracic surgery when control of bleeding by standard surgical methods of hemostasis (e.g. suture, ligature, and cautery) is ineffective or impractical.

EVARREST is applied topically to tissue surfaces. The recommended dosage of EVARREST depends on the size of the bleeding surface to be covered.

Product Description:

EVARREST Fibrin Sealant Patch is a biologics/device, single-entity combination product. It is made of plasma-derived human fibrinogen and thrombin (biological components) coated onto a composite backing layer (device component). Both biological components, human fibrinogen and thrombin, are ----b(4)----- manufactured by Omrix under US license 1603.

The composite backing layer of EVARREST consists of an oxidized regenerated cellulose (ORC) layer under a layer of polyglactin 910 (PG910) non-woven fibers which contain the embedded biological components (Figure 1). The materials used for both components of the backing layer are used in other licensed products – ----b(4)-----

EVARREST is supplied in 4 x 4 inch (10.2 x 10.2 cm) absorbable patches, the active side is white-to-yellow in color and powdery in appearance, and the non-active side has an embossed wave pattern. Each patch contains 50.3 mg/inch² (7.8 mg/cm²) of human fibrinogen, 203.2 IU/inch² (31.5 IU/cm²) of human thrombin, and -b(4)- of the backing layer. The ORC component constitutes -b(4)- of the patch mass.

Composition of EVARREST Fibrin Sealant Patch:

Table 1 Composition of Fibrin Sealant Patch				
<u>Components</u>	<u>Average Value</u>			<u>Function</u>
	<u>Per in²</u>	<u>Per cm²</u>	<u>% of patch mass</u>	
Backing Layer	-b(4)--	-b(4)--	-b(4)-- ORC: -b(4)- PG910: -b(4)-	Backing and Carrier
Human Fibrinogen	50.3 mg	7.8 mg	-b(4)-	Active Ingredient
Human Thrombin	203.2 IU	31.5 IU		Active Ingredient

EVARREST is sterilized by electron-beam irradiation after completion of inner and outer packaging resulting in a sterile product in a sterile inner package.

Figure 1 EVARREST BioActive Matrix



Mechanism of Action of EVARREST:

The primary mode of action for EVARREST to achieve and maintain hemostasis is provided by the fibrin sealant component of the product. Fibrinogen and thrombin are the first components to contact the wound surface and be hydrated. Their subsequent interaction in the cascade of biochemical reactions results in the formation of the fibrin clot.

The device component (current agreed-upon term: “the backing layer”; previous term “matrix”) is viewed as a delivery mode for the biological components to the wound site. The backing layer imparts inherent mechanical integrity to the product; the formed fibrin clot integrates with the backing layer to adhere to the wound surface and provide a physical barrier to bleeding. The pliability of the backing layer accommodates the physiological movements of tissues and organs.

While the ORC backbone has a “passive” hemostatic capability of its own, --b(4)-----
-----(------b(4)-----) and EVARREST
(a biologics/device combination product with –b(4)- ORC) are two different products with
different mechanisms of action. –b(4)-----requires that ----b(4)-----
----- By contrast, EVARREST achieves hemostasis due to the presence of the
fibrin sealant component. Noteworthy, the biological substances are applied onto the PG910 side
of the composite layer and are not in direct contact with the ORC side. The specifics of
EVARREST structure partially lessen the concern of potential adhesion formation.

Resolution of Issue by the Review Committee:

1. September 4, 2012 telecon with Herbert Lerner (CDRH, Sup. Medical Officer Ob Gyn Devices Branch, Division of Reproductive, Gastro-Renal and Urological Devices). CBER members present at the telecon: Nisha Jain, Kimberly Lindsey, Tim Lee, and Natalya Ananyeva.
 - CBER informed CDRH that the BLA reviewers are aware of the adhesiogenic concern, and adhesion warning/precaution is included in the current draft of the Prescribing Information - section 5.4.

- Dr. Lerner seemed to be relieved to know that CBER reviewers have taken steps to address this concern in the Prescribing Information.
2. Considerations for path forward:
- Emphasize potential for adhesions in the presence of blood in the Warnings and Precautions sections.
 - Consider a “limitations for use” statement for gynecological procedures- (only 4 subjects who underwent soft tissue surgery had a total abdominal hysterectomy/bilateral salpingo-oophorectomy, i.e.TAH/BSO).

Recommendation from the OBRR Upper Management:

Dr. Epstein supported the steps taken by the Review Committee to resolve the CDRH concern related to potential adhesion formation with the use EVARREST. Dr. Epstein recommended including the “adhesion” statement in the Prescribing Information for EVARREST as a limitation of use. If additional information is provided by Ethicon to lessen this concern, the statement with appropriate language can be included under “Warnings and Precautions”.