

Summary Basis for Regulatory Action

Date	November XX, 2012
From	Natalya Ananyeva, Ph.D., Committee Chairperson
Subject	Summary Basis for Regulatory Action
BLA #	STN 125392/0
Applicant	Ethicon, Inc.
Date of Submission	October 9, 2012 (Response to the CR letter dated 28 September 2012)
PDUFA Goal Date	December 9, 2012
Proprietary Name / Established names	EVARREST / Fibrin Sealant Patch
Dosage forms	<p>Package size: Each carton contains one 4 x 4 inch (10.2 x 10.2 cm) patch of EVARREST.</p> <p>Strength: Each 4 x 4 inch (10.2 x 10.2 cm) patch of EVARREST contains 50.3 mg per square inch (7.8 mg per square cm) of human fibrinogen and 203.2 units per square inch (31.5 units per square cm) of human thrombin.</p> <p>Apply on the surface of tissue only. Not to be used intravascularly.</p> <p>The number of EVARREST patches to be applied should be determined by the size of the bleeding surface.</p>
Proposed Indication	For use with manual compression as an adjunct to hemostasis 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, cautery) is ineffective or impractical.
Orphan Designation	No
Recommended Action:	Approval
Signatory Authorities Action	<p>Jay S. Epstein, M.D. _____ <i>Offices Signatory Authority:</i></p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p> <p><input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i></p> <p><input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i></p> <p>Mary Malarkey _____ <i>Offices Signatory Authority:</i></p> <p><input type="checkbox"/> <i>I concur with the summary review</i></p>

	<input type="checkbox"/> <i>I concur with the summary review and include a separate review or addendum to add further analysis</i> <input type="checkbox"/> <i>I do not concur with the summary review and include a separate review or addendum</i>
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Material Reviewed	Reviewers and Consultants
Clinical	Kimberly Lindsey
Bio-Statistics	John Scott
Pharmacology/Toxicology	La’Nissa Brown-Baker
CMC - Product	Natalya Ananyeva (Chairperson) & Nancy Kirschbaum
CMC - Facility	Randa Melhem & Nancy Waites
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Labeling	Loan Nguyen & Kristine Khuc
Epidemiology	Faith Barash
Lot Release Testing Plan	Karen Campbell
Regulatory Project Manager:	Tracy Tilghman & Mark Shields
Clinical Pharmacology	Not applicable
Advisory Committee	Not presented

1. Introduction

Ethicon Inc./Omrix Biopharmaceuticals Ltd. submitted an original Biologics License Application (BLA) for a ready-to-use, sterile, bio-absorbable hemostatic agent, Fibrin Sealant Patch*, with the proprietary name EVARREST. EVARREST is a biologics/device combination product consisting of plasma-derived Human Fibrinogen and Thrombin (biologics components) coated onto a backing layer (device component). The backing layer consists of an oxidized regenerated cellulose (ORC) layer underlying a layer of polyglactin 910 (PG910) non-woven fibers. The PG910 side contains the embedded biologics components.

EVARREST is supplied in 4 x 4 inch (10.2 x 10.2 cm) patches, with the active side being white-to-yellowish in color and powdery in appearance, and the non-active side having an embossed wave pattern. Each patch of EVARREST contains nominally 50.3 mg/in² (7.8 mg/cm²) of Fibrinogen and 203.2 IU/in² (31.5 IU/cm²) of Thrombin.

EVARREST is indicated for use with manual compression as an adjunct to hemostasis 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, cautery) is ineffective or impractical.

Ethicon conducted four clinical trials to support the efficacy and safety of EVARREST. One study in soft tissue surgery was conducted under a United States Investigational New Drug Application (IND). Additional studies included a second soft tissue surgery study, and hepatic resection and renal surgery studies that were conducted outside of the U.S. and not under IND.

* Throughout the summary, Fibrin Sealant Patch (the proper name), Fibrin Pad (the term used during product development and in pre-clinical and clinical studies) and EVARREST (the proprietary name) are used interchangeably.

2. Background

Fibrin sealants mimic the final stage of the blood coagulation cascade via the combination of concentrated solutions of thrombin and fibrinogen. The two-component fibrin sealants, in frozen liquid or lyophilized forms, have a long history of clinical use, including FDA-licensed products – TISSEEL and ARTISS (Baxter Healthcare Corp.), and EVICEL (Omrix Biopharmaceuticals Ltd.).

The underlying concept for EVARREST is to combine the hemostatic properties of fibrin sealants with the mechanical integrity and strength of the backing layer to promote rapid and targeted hemostasis at the wound site. The flexibility of the backing layer accommodates the physiological movements of tissues and organs. In this class of combination fibrin sealant products, EVARREST is the second product seeking U.S. licensure. A similar product, TachoSil from Nycomed, Austria (currently Takeda Pharmaceuticals Intl.) was approved by FDA under STN 125351/0 in April 2010 (U.S. license 1825).

Both biologics components, Human Fibrinogen and Thrombin, are -----
 --(b)(4)-----, manufactured by Omrix Biopharmaceuticals Ltd.
 (Omrix) under U.S. license 1603.

The materials used for both components of the backing layer - oxidized regenerated cellulose and PG910 p0lymer fiber - -----
 -----(b)(4)-----

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Table 1. Composition of EVARREST 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

During surgery, surgeons may encounter bleeding that is difficult to control because of the anatomic location, proximity of adjacent structures, or tissue type. There are many primary methods available for the prevention and treatment of such bleeding when it is encountered. The methods include ligature, suture, staples, packing and energy based coagulation (e.g., electrocautery, argon beam laser, and ultrasound). Fibrin Sealant Patches are used as an adjunct to these primary methods.

3. Chemistry, Manufacturing and Controls (CMC): Product and Facilities

Manufacture

The manufacture of EVARREST Final Product includes (i) the manufacture and further preparation of the Biologics Drug Substances - plasma-derived Human Fibrinogen and Thrombin; (ii) the manufacture of the backing layer, and (iii) the production of the Fibrin Sealant (FS) Patch, i.e., coating the backing layer with a suspension of the biological substances. Human Fibrinogen and Thrombin are active ingredients and their manufacturing processes were reviewed for the licensure -----(b)(4)------. The subsequent steps in the manufacture of EVARREST FS Patch were reviewed under the current BLA and are described below. The manufacture of EVARREST FS Patch is a bioburden-controlled process performed with aseptic techniques.

Preparation of the Biological Substances

The design and manufacture of Human Fibrinogen and Human Thrombin comply with cGMP regulations as specified in 21 CFR 210, 211, and 600 through 680. Both Drug Substances are manufactured at Omrix's -----(b)(4)-----
----- Israel. The starting material for Human Fibrinogen
(----- (b)(4) -----) is manufactured from human Source Plasma collected from qualified donors in FDA-licensed facilities in the United States or alternatively purchased from -----
--(b)(4)-----, an FDA-approved supplier (U.S. License # (b)(4)). The starting material for Human Thrombin (----- (b)(4) -----) is derived from human Source Plasma
----- (b)(4) ----- collected from qualified donors in FDA-licensed facilities in the United States.

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Manufacture of the Backing Layer

The composite backing layer is made of two absorbable polymers - oxidized regenerated cellulose (ORC) and polyglactin 910 (PG910). The backing layer is manufactured by -----
----- (b)(4) -----
----- . The design and manufacture of the backing layer comply with the
Quality System regulations as specified in 21 CFR Part 820. The patch is produced in 4 x 4 inch
units, ----- (b)(4) ----- . In the backing layer, nominal amounts for PG910 are ----- (b)(4) -----
----- and for ORC – ----- (b)(4) ----- that yield a total backing layer content of -----
(b)(4) ----- .

----- (b)(4) -----

----- (b)(4) -----

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Application of Drug Substances to the Backing Layer

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Sterilization Process

The final step in the FS Patch manufacturing process is terminal sterilization by electron beam (electron-beam) irradiation at a dose of ----(b)(4)----. The product is sterilized at -----
----- (b)(4) -----, a U.S.-licensed contract facility.

The validation of the sterilization process was performed with a simulated product using -(b)(4)-- as the biological component that underwent the identical manufacturing processes as the Fibrin Sealant Patch. The comparability of the simulated product to the FS Patch product was demonstrated in a microbial growth comparison test.

The validation included the following studies:

1. An -----(b)(4)----- dose-setting experiment was performed to establish the minimum dose requirement for sterilization of the Fibrin Sealant Patch to achieve a sterility assurance level ----(b)(4)----. With a range of irradiation doses tested, a minimum dose requirement of --(b)(4)-- was established to ensure sterility. In product qualification studies, a maximum dose of ---(b)(4)--- was established to minimize the exposure of the proteins to excessive irradiation.
2. Dose-mapping studies were performed to establish the parameters of electron beam processing required to satisfy the absorbed dose requirements for the 4 x 4 inch Fibrin Sealant Patch product, and to demonstrate that the absorbed dose requirements are repeatable and reproducible. The final product is irradiated ----(b)(4)----.
3. The effect of electron-beam irradiation on the Fibrin Sealant Patch was evaluated by:
 - -----(b)(4)-----
 - -----(b)(4)-----
 - -----(b)(4)-----
 - -----(b)(4)-----

----- (b)(4) -----

----- Potential immunogenicity of EVARREST as a result of electron-beam irradiation was assessed in pre-clinical and clinical studies. In clinical studies, the proportion of subjects having an immune response to thrombin component of FS Patch was similar to that

reported in the literature for patients treated with other human thrombin products. There was only transient or no immune response to fibrinogen (please refer to section 7c). Additional data on potential immunogenicity of EVARREST are being obtained in ongoing studies in different clinical settings under U.S. IND.

The loss of Thrombin Activity during the manufacturing process is monitored and controlled by:

- Established correlation between the target input dose and Thrombin Activity measured in the Final Product;
- -----(b)(4)-----
- Final release testing of irradiated FS Patch (specification range of -----(b)(4)-----).

Dose Optimization

----- (b)(4) -----

- ----- (b)(4) -----

- ----- (b)(4) -----);
- ----- (b)(4) -----

----- (b)(4) -----

Coating Uniformity

----- (b)(4) -----

Control of Fibrinogen-Thrombin Reaction on FS Patch at Release and throughout its Shelf Life

Release Specifications of Fibrin Sealant Patch

Tests	Acceptance Criteria	
	US Units	Metric Units
Identity		
Appearance	Complies ^a	Complies ^a
Potency		
------(b)(4)-----	------(b)(4)-----	------(b)(4)-----
------(b)(4)-----	------(b)(4)-----	------(b)(4)-----
Thrombin Activity	------(b)(4)-----	------(b)(4)-----
-----(b)(4)----	------(b)(4)-----	------(b)(4)-----
Purity/Impurities		
------(b)(4)-----	--(b)(4)--	--(b)(4)--
------(b)(4)-----	------(b)(4)-----	------(b)(4)-----
Endotoxin	------(b)(4)-----	------(b)(4)-----
Sterility	Sterile	Sterile
Irradiation Dose ^b	------(b)(4)-----	------(b)(4)-----
Packaging Integrity (b)(4) Test	------(b)(4)-----	------(b)(4)-----
Visual Inspection of Foil Pouch Seal Integrity	Complies ^c	Complies ^c

^a The active side is powdery and white to yellowish in color.

The non-active side is white to yellowish in color with an embossed waved pattern.

^b The result is obtained from irradiation certification as determined by ---(b)(4)---.

^c Pouch seal is clear of non-conformances in visual inspection.

Batch Analysis

 -----(b)(4)-----

Table 2. Virus Reduction Factors for Human Fibrinogen

Manufacturing Step	Reduction Factor (Log ₁₀) of virus tested					
	Enveloped Viruses*			Non-enveloped Viruses**		
	HIV-1	BVDV	PRV	EMCV	HAV	CPV
S/D Treatment	> 4.42	> 4.39	> 3.96	Not Tested	Not Tested	0.0
Pasteurization	> 4.39	> 5.46	6.0	3.69	> 5.78	1.33
Cumulative virus Reduction Factor	> 8.81	> 9.85	> 9.96	3.69	> 5.78	1.33

- * HIV-1: Human Immunodeficiency Virus Type 1
- BVDV: Bovine Viral Diarrhea Virus
- PRV: Pseudorabies Virus
- **EMCV: Encephalomyocarditis Virus
- HAV: Hepatitis A Virus
- CPV: Canine Parvovirus

Table 3. Virus Reduction Factors for Human Thrombin

Manufacturing Step	Reduction Factor (log ₁₀) of virus tested						
	Enveloped Viruses*				Non Enveloped Viruses**		
	HIV-1	SBV	BVDV	PRV	EMCV	HAV	CPV
S/D Treatment	> 5.82	> 5.31	> 4.74	> 4.25	Not Tested	Not Tested	0.0
Nanofiltration	> 4.36	> 5.32	Not Tested	> 5.47	6.37	6.95	5.85
Cumulative virus Reduction Factor	> 10.18	> 10.63	> 4.74	> 9.72	6.37	6.95	5.85

- * HIV-1: Human Immunodeficiency Virus Type 1
- SBV: Sindbis Virus
- BVDV: Bovine Viral Diarrhea Virus
- PRV: Pseudorabies Virus
- **EMCV: Encephalomyocarditis Virus
- HAV: Hepatitis A Virus
- CPV: Canine Parvovirus

Transmissible Spongiform Encephalopathy

The safety of EVARREST with regard to prions is based on strict plasma donor selection criteria employed in FDA-licensed donation centers in the United States. The risk to transmit vCJD has been assessed by FDA/PHS (the CBER website) to be small. -----

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----- (b)(4) -----

----- (b)(4) -----

Inspection of the Manufacturing Facilities

The Center for Biologics Evaluation and Research (CBER) performed a Pre-License Inspection (PLI) of Omrix Biopharmaceuticals Ltd. (b)(4) and FPPF facilities (Israel) from May 10th to May 19th, 2011. ----- (b)(4) -----, whereas this was the first FDA inspection for the FPPF. -----

----- (b)(4) -----

The announced PLI for (b)(4) in Israel covered the evaluation of the manufacture of Human Thrombin and Human Fibrinogen Drug Substances at ----- (b)(4) -----, and the manufacture of the Fibrin Sealant Patch final product at FPPF including ----- (b)(4) ----- of the Drug Substances followed by ----- (b)(4) -----, and the application of the protein intermediates onto the backing layer using the ----- (b)(4) ----- process followed by primary packaging, ----- (b)(4) ----- and secondary packaging. The Fibrin Sealant Patch manufacturing at FPPF is a bioburden controlled process. The May 2011 inspection covered Quality, Production, Facility & Equipment, Materials Management, and Support Systems with respect to the manufacture of the Fibrin Sealant Patch.

A nine-item Form FDA 483 was issued for objectionable conditions observed during the inspection at the (b)(4), and an eight-item Form FDA 483 was issued for objectionable conditions observed during the inspection at the FPPF on May 19th, 2012. The observations included inadequate cleaning validations and programs for facility and equipment, inadequate environmental monitoring program, inadequate qualification of equipment (----- (b)(4) -----), Special Processing Request procedure that allows for the implementation of deviations to the established manufacturing process without performing adequate documentation of the deviation and formal tracking of the occurrence, and inadequate shipping validation and procedures.

The Firm submitted their initial responses to the 483 observations in June and August 2011 which reported the progress towards completion of the corrective actions to the 483 observations. Upon review, a Complete Response letter was issued on 19 September 2012 that included these observations as deficiencies.

In their Complete Response to the CR letter dated March 30th, 2012, the Firm provided description of the corrective actions to the observations listed on the Form FDA 483 for each facility, and most of responses were found adequate. One remaining item is addressed in a Post Marketing Commitment (PMC), which is related to the ----- (b)(4) ----- . The PMC final report will be

submitted to the FDA in February 2013. Please refer to section 14. Post Marketing Commitments for details.

Environmental assessment

The BLA included a request for a categorical exclusion for an Environmental Assessment under 21 CFR § 25.31(c). The FDA concluded that this request is justified, as the active ingredients of the proposed product are naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

Conclusion:

The manufacturing process for the EVARREST Fibrin Sealant Patch is validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of the product that meets Release Specifications. The manufacturing processes for Biological Substances and Final Product provide acceptable safety margins regarding adventitious agents. The inspection-related issues have been adequately addressed in Ethicon's responses to the CR letter. The remaining one inspectional and two product-related items are addressed in Post Marketing Commitments. The Product and Facility reviewers conclude that Ethicon has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of the EVARREST Fibrin Sealant Patch.

4. Non-clinical Pharmacology/Toxicology

a) Pharmacological/Toxicological Findings

EVARREST was determined to be safe for its intended use as an adjunctive hemostat, based on data from non-clinical studies (Good Laboratory Practices [GLP] and non-GLP compliant), and its clinical use in surgical settings.

The non-clinical program consisted of a series of studies to demonstrate the safety and effectiveness of EVARREST. EVARREST was evaluated in controlled non-clinical studies, according to its intended clinical use (i.e., as an adjunct to hemostasis). 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). These studies compared the safety and effectiveness of the EVARREST fibrin sealant patch with other adjunctive hemostatic methods (manual compression, or another cleared or approved hemostatic product) used as controls. Adverse findings were reported in both the control and EVARREST arms, including thromboembolic events, re-bleeding at treatment bleeding site, persistent inflammation, hemorrhage at wound site, and adhesion formation at treatment bleeding site. These adverse findings could be expected based on EVARREST mechanism of action, were predictive of adverse reactions reported in the clinical trials, and were similar in incidence to previous experience with analogous products (i.e., post-operative re-bleeding, neutralizing antibody formation, and thromboembolic events).

Long-term animal studies to evaluate the carcinogenic potential of EVARREST or studies to determine its genotoxicity or effects on fertility have not been performed. Ethicon has completed an assessment of the carcinogenic risk of the EVARREST fibrin sealant patch to address potential long-term adverse effects from product use. The information submitted to the BLA suggests that the carcinogenic potential of this product should be minimal.

b) Pharmacokinetics

EVARREST was acutely tested in animals at up to 10 times the intended clinical dose (approximately 1 standard size pad/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 (< 10% of patch remaining in animal studies), with remnants degrading exponentially.

Conclusion:

The non-clinical safety profile determined for EVARREST Fibrin Sealant Patch is sufficient to support the safe use of EVARREST in the proposed indication as an adjunct to hemostasis.

5. Clinical Pharmacology

a) Mechanism of Action

EVARREST is made of two biological components (human plasma-derived fibrinogen and human plasma-derived thrombin) embedded in a flexible composite backing layer. The backing layer provides a large surface area for the biological components and imparts mechanical integrity to the product. The flexibility of EVARREST accommodates the physiological movements of tissues and organs.

The mechanism of action of EVARREST is based on the interaction between the biological components, which follows the principles of physiological fibrin clot formation. Upon contact with a bleeding wound surface, the biological components embedded in the backing layer are hydrated, and the subsequent fibrinogen-thrombin reaction initiates the last step in the cascade of biochemical reactions - conversion of fibrinogen into fibrin monomers that further polymerize to form the fibrin clot. Hemostasis is achieved when the formed fibrin clot integrates with the backing layer to adhere to the wound surface and provide a physical barrier to bleeding.

6. Clinical/Statistical

a) Clinical Program

Ethicon conducted four clinical trials to support the safety and efficacy of EVARREST, when used as an adjunct to hemostasis. Studies 400-07-002, 400-08-002 evaluated the use of

EVARREST as an adjunct to hemostasis in soft tissue (intra-abdominal, retroperitoneal, pelvic, and non-cardiac thoracic surgical procedures). Study 400-10-001 evaluated the use of EVARREST as an adjunct to hemostasis during hepatic resection procedures. A ten (10) subject phase 1 study was conducted in subjects undergoing surgery for partial nephrectomy.

b) Review of Clinical Data

The primary study submitted as the basis for approval was Study 400-07-002, a prospective, multi-center (U.S. sites only), randomized trial including 141 subjects of median age 62 years (range 26 to 89 years), conducted to compare the safety and efficacy of EVARREST with that of oxidized regenerated cellulose (ORC), an absorbable hemostat, when used as an adjunct to control bleeding after primary methods to achieve hemostasis (suture, cautery, ligature) proved ineffective or impractical during open abdominal, pelvic, retroperitoneal, and non-cardiac thoracic surgery. EVARREST or ORC was applied immediately to the actively bleeding Target Bleeding Site (TBS). Manual compression was applied continuously for each treatment group until 4 minutes post randomization. Hemostasis was assessed at 4 minutes from randomization, and following an additional 6 minute observational period. Success was defined as the achievement of hemostasis at 4 minutes and no further bleeding requiring treatment during the additional 6 minute observation period.

A total of 90 subjects were randomized into the trial in a 2:1 ratio (60 treated with EVARREST, 30 treated with ORC). Additional 51 subjects were treated with EVARREST during a subsequent non-randomized phase, which provided additional safety data.

Efficacy Endpoints

The primary endpoint of the study was the “proportion of subjects achieving hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6 minute observation period”. Hemostatic success was defined as no detectable bleeding at the TBS.

EVARREST was shown to have a statistically significant difference compared to ORC, 98.3% vs. 53.3% ($p < 0.0001$), in the proportion of subjects achieving hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6-minute observation period.

Table 4. Proportion (%) of Subjects Achieving Hemostasis at 4 minutes

EVARREST	ORC	p-value	Treatment Difference
59/60 (98.3%)	16/30 (53.3%)	<0.0001	45.0%

The efficacy data for the 51 non-randomized subjects treated with EVARREST were supportive of the above efficacy findings with 50/51 subjects (98.0 %) achieving hemostatic success at 4 minutes after randomization with no re-bleeding requiring treatment during a subsequent 6-minute observation period.

The secondary efficacy endpoints for study 400-07-002 were:

- Proportion of subjects achieving hemostatic success at the TBS at 10 minutes following randomization (Success at 10 minutes was defined as the achievement of hemostasis within 10 minutes and no further bleeding requiring treatment during the final 6-minute observation period);
- Incidence of treatment failures (if hemostasis was not achieved within 4 minutes or if bleeding requiring additional intervention occurred during the 6 minute observation period);
- Incidence of re-treatment at TBS.

These endpoints and the treatment effects are summarized in the table below and were favorable towards EVARREST.

Table 5. Secondary Effectiveness - Intent-to-Treat Analysis Set

Variable	Category	Treatment	
		Fibrin Pad (N=60)	ORC (N=30)
Success at 10 min (secondary)	Yes	59 (98.3%)	22 (73.3%)
	No	1 (1.7%)	8 (26.7%)
Treatment failure	Yes	1 (1.7%)	14 (46.7%)
	No	59(98.3%)	16 (53.3%)
Any TBS retreatment (including SoC)	Yes	1 (1.7%)	14 (46.7%)
	No	59 (98.3%)	16 (53.3%)

Efficacy Conclusion:

The clinical trial conducted to support the proposed indication for EVARREST met the pre-specified primary endpoint in that EVARREST as an adjunct to hemostasis was superior to the comparator product by having a higher proportion of subjects achieving hemostatic success at 4 minutes. Advantages of FS Patch relative to the comparator product were also recorded on the secondary endpoints of 10-minute hemostasis, treatment failure, and TBS retreatment.

7. Safety

a) Safety Summary

Review of the safety data from the study 400-07-002 revealed an unfavorable trend against EVARREST with regards to thrombotic events (TEs). In the non-randomized part of the study 400-07-002, a total of seven venous TEs (five pulmonary emboli and two deep vein thromboses, please refer to Table 6) were reported in seven subjects of 51 subjects enrolled in this study. As the clusters of TEs were seen in the non-randomized, uncontrolled part of the study, it was not possible to draw a conclusion regarding the association of the investigational product with these AEs. The Applicant also submitted the data from a second soft tissue surgery study, Study 400-08-002 (a non-IND study), that had a similar design to study 400-07-002. However, the safety data captured under this study did not adequately address FDA’s concerns with regard to the AEs seen in the 400-07-002 because it was unclear if the patients were adequately monitored to capture the TEs, infections, abscesses, and adhesions.

These safety concerns led to the issuance of the first complete response (CR) letter. FDA requested additional safety data to assess whether or not the imbalances in the adverse events seen in the study 400-07-002 would have occurred by chance based on the size of the study, and to assess the causality of these events. Ethicon submitted additional safety data from a study in patients undergoing hepatic resection surgery (Study 400-10-001). As safety related to product use is unlikely to be different in hepatic surgery patients, the data can be considered supportive for overall safety assessment, especially with regard to thrombosis. The total safety database for EVARREST used as an adjunct to hemostasis consists of 239 subjects from the four clinical studies:

1.) Study 400-07-002: One hundred and eleven (111) subjects were treated with EVARREST during a randomized, controlled superiority study comparing the safety and efficacy of EVARREST with oxidized regenerated cellulose (ORC) when used as an adjunct to hemostasis for mild to moderate soft tissue bleeding in subjects undergoing abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery. Of these, 60 subjects were treated with EVARREST during the randomized, comparative phase of the study and 51 were treated during the subsequent non-randomized phase during which all subjects received treatment with EVARREST.

2.) Study 400-08-002: Fifty nine (59) subjects treated with EVARREST in this randomized, controlled, superiority non-IND study conducted outside the US, evaluated the efficacy of EVARREST compared with Standard of Care (SoC) methods utilized to control soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery for which standard methods of achieving hemostasis were ineffective or impractical. Subjects who met the eligibility criteria were randomized 2:1 EVARREST vs. SoC Control. The primary endpoint was the proportion of subjects achieving hemostasis at the TBS at 4-minutes following randomization and with no re-bleeding at the TBS any time prior to initiation of wound closure time. The post operative follow up period was 60 days.

3.) Study 400-10-001: Of fifty nine (59) subjects who were treated with EVARREST in this study, thirty nine (39) were treated in a randomized, controlled, superiority non-IND study conducted outside the US evaluated the efficacy of EVARREST to the Standard of Care methods commonly used to control bleeding in the hepatic parenchyma after standard methods to control bleeding were deemed ineffective, impractical or inappropriate.

The TBS was defined as the “first actively bleeding site identified in the hepatic parenchyma after completion of parenchymal transection not responsive to 30 seconds of manual compression alone. The bleeding site also had to exhibit persistent bleeding requiring the surgeon’s immediate attention because conventional methods to achieve hemostasis failed or were impractical or inappropriate, thus necessitating an alternative hemostatic method. The primary endpoint was the proportion of subjects achieving hemostasis at the TBS at 4-minutes following randomization and with no re-bleeding at the TBS any time prior to initiation of wound closure (last point in time where EVARREST was visible to confirm hemostasis). The post operative follow up period was 60 days.

4.) Study FL-PN-001-IS: Ten (10) subjects undergoing surgery for partial nephrectomy were treated in this non-IND phase 1 study conducted in Israel.

Therefore, the safety database considered to support the use of EVARREST as an adjunct to hemostasis consists of a total of 239 subjects who have been treated with EVARREST in 4 clinical studies.

b) Adverse Reactions

EVARREST was used as an adjunct to hemostasis to treat soft tissue (retroperitoneal, intra-abdominal, pelvic, or thoracic) or parenchymal (hepatic or renal) surgical bleeding in clinical trials involving 239 subjects treated with EVARREST and 110 control subjects. Of the 239 subjects treated with EVARREST, 229 subjects were those enrolled in three pivotal studies 400-07-002, 400-08-002, and 400-10-001, with 107 control subjects. Thirty-one percent (31%) of treated subjects (71 subjects of 229) and 33% of control subjects (35 subjects of 107) experienced one or more serious adverse reactions. Table 6 shows the adverse reactions in subjects treated with EVARREST in the controlled (randomized) and uncontrolled (non-randomized) portions of the individual pivotal trials used to support safety of EVARREST. Adverse reactions are summarized by organ system class and MedDRA preferred term. The most frequent reactions were pleural effusion, abdominal distension, pulmonary embolism, localized intra-abdominal fluid collection, increased blood fibrinogen, post procedural and intra-abdominal hemorrhage, and ascites. Other serious adverse reactions included deep vein thrombosis.

Table 6. Adverse Reactions in Individual Studies based on MedDRA Preferred Term

Adverse Reaction ¹ (MedDRA preferred term)	Study 400-07-002			Study 400-08-002		Study 400-10-001			Total	
	EVARREST Randomized and non Randomized N ² = 111 n (%)	EVARREST Randomized N=60 n (%)	Control N ² = 30 n (%)	EVARREST Randomized N ² = 59 n (%)	Control N ² =32 n (%)	EVARREST Randomized and non Randomized N ² = 59 n (%)	EVARREST Randomized N =39 n (%)	Control N ² = 45 n (%)	EVARREST All Subjects ³ N ² =229 n (%)	Control ² N=107 n (%)
Deaths	6 (5.4%)	2 (3.3%)	1 (3.3%)	4 (6.8%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (4.3%)	4 (3.7%)
Pleural effusion	17 (15.3%)	12 (20.0%)	5 (16.7%)	9 (15.3%)	7 (21.9%)	7 (11.9%)	4 (10.3%)	8 (17.8%)	33 (14.4%)	20 (18.7%)
Abdominal distension	4 (3.6%)	0 (0.0%)	0 (0.0%)	4 (6.8%)	1 (3.1%)	1 (1.7%)	1 (2.6%)	0 (0.0%)	9 (3.9%)	1 (0.9%)
Pulmonary embolism	5 (4.5%)	1 (1.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (2.6%)	0 (0.0%)	6 (2.6%)	1 (0.9%)
Localized intra-abdominal fluid collection	1 (0.9%)	1 (1.7%)	0 (0.0%)	1 (1.7%)	2 (6.3%)	2 (3.4%)	0 (0.0%)	6 (13.3%)	4 (1.7%)	8 (7.5%)
Blood fibrinogen increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.3%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.7%)	2 (1.9%)
Post procedural hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.4%)	0 (0.0%)	1 (1.7%)	1 (2.6%)	0 (0.0%)	3 (1.3%)	0 (0.0%)
Ascites	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (1.7%)	1 (2.6%)	2 (4.4%)	3 (1.3%)	2 (1.9%)
Deep venous thrombosis	2 (1.8%)	2 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	1 (0.9%)
Intra-abdominal hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.4%)	2 (5.1%)	0 (0.0%)	2 (0.87%)	0 (0.0%)
Operative hemorrhage	1 (0.9%)	0 (0.0%)	3 (10%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	1 (2.2%)	2 (0.9%)	4 (3.7%)
Gastrointestinal hemorrhage	1 (0.9%)	1 (1.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.9%)
Aspiration	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.7%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (1.9%)

¹ The table presents the number of patients experiencing at least 1 adverse reaction. For the summary tabulation, please note that a patient is counted once regardless of whether the patient had one or more adverse reactions reported.

² As treated population (safety data set).

³ FP All includes 158 FP randomized subjects and 71FP non- randomized.

The overall incidence of deaths was approximately 4% for both the EVARREST and control groups. Most subjects enrolled in these clinical trials had a major surgery, underlying malignancy and cardiovascular disease. FDA carefully reviewed the death narratives and case report forms and concluded that the deaths were unlikely to be due to the hemostatic treatment with EVARREST or Standard of Care, but rather consistent with the underlying disease condition of the patient population.

As follows from Table 6, the incidence of most adverse reactions was higher in the control group compared to the EVARREST group. An unfavorable trend in the EVARREST treatment arm was seen in pulmonary embolism (PE) adverse reactions. FDA reviewed case report forms and narratives for subjects with the PE and assessed the relationship of thrombotic / thromboembolic events to baseline demographics, operative procedure, anatomical location of operative procedures and target bleeding sites. The unfavorable trend against EVARREST reported from Study 400-07-002 was related to the imbalance in the PE reactions seen in the non-randomized, uncontrolled part of the study. Of the five (5) subjects in the EVARREST treatment arm who experienced the PE in this study, two (2) subjects had the PE within 2 days of the surgical procedure, one (1) subject had a “suspected” PE on the day of surgery with no computerized tomographic confirmation of the embolism, and the remaining two (2) subjects experienced the PE at days 15 and 20 post surgery.

Based on the EVARREST mechanism of action, FDA concluded that only those PE adverse reactions seen within 2 days of the surgical procedure in the two subjects could plausibly have a causal relationship to treatment with EVARREST. For the remaining subjects, other factors (radiographic evidence, temporal relationship, underlying malignancy, smoking history, diabetes, cardiovascular disease) were a more likely cause of the PE.

Considering that most subjects included in the studies had underlying malignancies, FDA reviewed the surgical literature for a venous thromboembolism rate among cancer patients. This reported background rate is within a 3-5% ¹ range, and is comparable to the overall incidence of the PE adverse reactions seen across all studies with EVARREST.

As the clustering of the PE reactions was associated with the use of EVARREST Lot M06F164, the Applicant performed extensive analytical characterization of this lot. FDA reviewed the results of evaluation of in-process control, release, and stability-indicating parameters of Lot M06F164 in comparison with other lots used in clinical studies and did not identify any differences that could be considered relevant to the safety or potential thrombogenicity of the product. In particular, Thrombin Activity -----(b)(4)----- were within the specification ranges, and -----(b)(4)----- analysis did not reveal the signs of protein degradation or aggregation at release and on stability. Upon review of the CMC information, FDA agrees with the conclusion of the Applicant that no plausible mechanisms were identified that could reasonably link the adverse events observed in the clinical study 400-07-002 to the product quality.

During the review, the safety data from the three studies were not pooled because of different clinical settings in which the product was used as well as different control agents used in the

studies. However, the safety data from each clinical setting can be considered supportive of the overall safety.

Table 7 summarizes the overall number of adverse reactions across all three clinical studies in the randomized subjects treated with EVARREST in comparison with the control subjects. A total of 158 randomized subjects were treated with EVARREST in controlled portions of these studies. Two studies also enrolled subjects who were not randomized and received treatment with EVARREST: 400-07-002 (N=51) and 400-10-01 (N=20).

Table 7: Summary of Adverse Reactions in Clinical Trials (400-07-002, 400-08-002 and 400-10-001)

	EVARREST Randomized (n=158)	Control (n=107)	EVARREST All Subjects¹ (n=229)
Adverse Reaction	n (%)	n (%)	n (%) ²
Pleural effusion	25 (15.8%)	20 (18.7%)	33 (14.4%)
Abdominal distension	5 (3.2%)	1(0.9%)	9 (3.9%)
Pulmonary embolism	1 (0.6%)	1 (0.9%)	6 (2.6%)
Localized intraabdominal fluid	2 (1.3%)	8 (7.5%)	4 (1.7%)
Blood fibrinogen increased	4 (2.5%)	2 (1.9%)	4 (1.7%)
Post procedural hemorrhage	3 (1.9%)	0 (0.0%)	3 (1.3%)
Ascites	2 (1.3%)	2 (1.9%)	3 (1.3%)
Deep vein thrombosis	0 (0.0%)	1 (0.9%)	2 (0.9%)
Intra-abdominal hemorrhage	2 (1.3%)	0 (0.0%)	2 (0.9%)
Operative hemorrhage	0 (0.0%)	4 (3.7%)	2 (0.9%)
Gastrointestinal hemorrhage	1 (0.6%)	1 (0.9%)	1 (0.4%)
Aspiration	1 (0.6%)	1 (0.9%)	1 (0.4%)

¹EVARREST All Subjects included 158 Randomized subjects and 71 Non-Randomized subjects

² The percent numbers were rounded in the Prescribing Information (section 11. Labeling).

Notably, the incidence of the PE in the randomized subjects treated with EVARREST (0.6%) is close to that in the control group (0.9%). Only those adverse reactions with an incidence (a) greater than or equal to 1%, and (b) greater in the EVARREST arm versus the control arm were included in the package insert (please refer to section 11. Labeling). In conclusion, FDA review of the totality of the evidence from all studies, including the clinical data, the CMC information and the published literature, suggests that the PE and other adverse reactions are likely to be related to the underlying conditions of the patient population and not to the hemostatic treatment with EVARREST. This analysis allows us to make a favorable decision for EVARREST regarding the potential risk/benefit balance.

Additional safety data for EVARREST are being obtained in ongoing studies in different clinical settings under U.S. IND.

¹Cronin, C., D. Lohan, et al. (2007). "Prevalence and significance of asymptomatic venous thromboembolic disease found on oncologic staging CT." *Am J Roentgenol.* **189**(1): 162-70.

- Each listed clinical investigator required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b), did not disclose any such interests; and
- No listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Bioresearch Monitoring (BIMO)

BIMO inspections of three clinical sites were performed in support of the BLA in January, March and April 2011, and were conducted in accordance with the FDA’s Compliance Program Guidance Manual (CPGM) 7348.811, Inspection Program for Clinical Investigators. The three sites enrolled 78 subjects, representing approximately 55% of the total subjects enrolled in Study 400-07-002.

Table 8. Results of BIMO Inspections

Site Number	Study Site	Location	Number of Subjects	Form FDA 483 Issued	Inspection Final Classification
011	R. Adams Cowley Shock Trauma Center	Baltimore, Maryland	18	Yes	VAI
014	Medical College of Georgia, Section of Urology	Augusta, Georgia	28	No	NAI
022	University of Alabama, Division of Cardiothoracic Surgery	Birmingham, Alabama	32	Yes	VAI

VAI – Voluntary Action Indicated

NAI- No Action Indicated

The BIMO summary memo was based on the Form FDA 483’s issued at the sites and discussions with the investigators. At two sites which received VAI letters, procedural deviations were noted and were stated in the Complete Response letter. However, it was concluded that the bioresearch monitoring inspections of the three clinical sites did not reveal problems that would impact the clinical data submitted in the application. The response letter from the Site 011 was received and was found to adequately address all of the BIMO non-compliance observations in the Form FDA 483.

8. Pediatric Research Equity Act (PREA)

PREA was triggered as a new indication was being sought. Ethicon requested a waiver from conducting pediatric studies in neonates (ages 0-28 days). The pediatric plan for a deferred study was presented to the Pediatric Review Committee (PeRC) on September 5th, 2012. The PeRC agreed with the Division to grant a deferral of pediatric studies for subjects ages 1 month to less than 17 years and a waiver for the neonatal pediatric population (0—28 days old). The neonatal population was waived because EVARREST may be ineffective or unsafe in this group of subjects due to the size limitations of the organs and inability to administer the product as described in the instructions for use (dosage and administration).

The Pediatric Use section of the Package Insert states, “The safety and effectiveness of EVARREST in pediatric subjects have not been established”; “Use of EVARREST in children under the age of one month may be unsafe or ineffective due to small size and limited ability to apply the patch as recommended. Slow absorption and possibility of adhesions can further complicate use of EVAREST in the neonates.” Additionally, since the neonatal surgical population often requires repeat operations for congenital abnormalities, use of EVARREST may be limited due to the fact that the surgical site to which the EVARREST patch would be applied may also be the site of a subsequent operation. Since EVARREST absorbs slowly and may cause adhesions, its use for repeat operations may not be advisable.

9. Advisory Committee Meeting

OBRR reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure is not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

1. New molecular entity provision does not apply to EVARREST as it does not represent a historically novel product class. Fibrin sealants have been used as an adjunct to hemostasis since the late 1970’s in Europe and since 1998 in the United States (TISSEEL manufactured by Baxter was approved by FDA in May 1998).
2. The mechanism of action of fibrin sealants (fibrinogen/thrombin products) and their function in blood coagulation and control of local hemorrhage is well studied and understood. Upon contact with the bleeding wound surface, the fibrinogen-thrombin reaction initiates the last step of the coagulation cascade – formation of a fibrin clot.
3. The Biological Components of EVARREST are ----- --
----- (b)(4) -----

----- The materials used for both components of
the backing layer are used in other licensed products: -----
----- (b)(4) -----

4. A similar combination fibrin sealant product, TachoSil (Takeda Pharmaceuticals / Nycomed), has been used in European Union since 2004 and was approved by FDA in 2010 (STN 125351) as an adjunct to hemostasis in cardiovascular surgery where standard techniques are insufficient.
5. The overall clinical program to evaluate efficacy and safety of EVARREST was adequate and did not raise any major concerns.
6. Review of information submitted in the BLA for EVARREST did not raise any controversial issues or pose unanswered scientific questions which would have benefited from advisory committee discussion and recommendation.

10. Pharmacovigilance

As part of the Pharmacovigilance plan (PVP), Ethicon should submit all reports of thrombotic events and events potentially related to post-surgical adhesion formation, including known adverse reactions listed in the EVARREST prescribing information and regardless of seriousness as 15-day reports. 15-Day “Alert Report” for Drugs and Biological Products : A reporter must submit to FDA a report of an adverse experience associated with the use of a drug or biological product that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 days of initial receipt of the information as set forth in §§ 314.80(c)(1) and (e), and 600.80(c)(1) and (e).

The Office of Biostatistics and Epidemiology does not recommend additional post marketing requirement / post marketing commitment (i.e., PMR/PMC) studies for immunogenicity or repeat exposure.

11. Labeling

a) Proprietary Name

The proposed proprietary name, **EVARREST**, for Fibrin Sealant Patch was reviewed at the time of initial submission by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective and was found to be acceptable.

On July 24th, 2012, APLB performed a re-evaluation of the proposed proprietary name, **EVARREST**, to determine if any new product had been approved since the previous review dated February 7th, 2011. APLB found that no products have been approved that would change their previous recommendation. APLB found the proprietary name **EVARREST** acceptable.

b) Prescribing Information

The text of Prescribing Information (PI) was originally reviewed during the period from 30 March 2012 to 28 September 2012, and was found not in compliance with 21 CFR 201.57. In particular, there were outstanding issues with

- the location of specific information (content) and format of the PI;
- incorrect use of a number of key terms;
- incorrect list and order in the Warnings and Precautions section;
- incorrect information in the Adverse Reactions section; and
- incomplete Drug Listing Data Elements in the SPL.

A second Complete Response letter was issued on 28 September 2012 citing these issues as deficiencies. The CR letter also included the recommended text of the Prescribing Information and the package label (please refer to section 11c).

Ethicon incorporated all the FDA recommendations in the respective labeling, and submitted the revised versions to the FDA as a complete response to the CR letter (received on 9 October 2012). The revised labeling was reviewed, and the latest version of Prescribing Information (29 November 2012) was found to be acceptable.

----- (b)(4) -----
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3. -----

----- (b)(4) -----

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In Amendment STN 125392/0.25 dated 6 September 2012, Ethicon, Inc. commits to the following:

4. ----- (b)(4) -----
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5. -----
----- (b)(4) -----
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No clinical PMC was requested because additional clinical studies are ongoing under Investigational New Drug application.