Summary Basis for Regulatory Action Template

Date: March 30, 2015

From: Charles Maplethorpe, M.D., Ph.D. Chair of the Review Committee

BLA/ STN#: 125392/33

Applicant Name: Ethicon, Inc.

Date of Submission: May 30, 2014

PDUFA Goal Date: March 30, 2015

Proprietary Name/ Established Name: EVARREST/Fibrin Sealant Patch

Indication: Adjunct to hemostasis for liver surgery parenchymal bleeding

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Paul Mintz, M.D, Director Division of Clinical Review

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Reviewer Name – Document(s) Date	**Specific documentation used in developing the SBRA**
Clinical Review	Charles Maplethorpe, M.D., Ph.D.
Statistical Review	Min Lin, Ph.D.
Pharmacology/ Toxicology Review	La'Nissa Brown-Baker, Ph.D.
Bioresearch Monitoring Review	Bioresearch monitoring inspections were not conducted for this BLA

1. Introduction

STN125392/33 is a clinical supplement to add the adult liver surgery indication to the label for EVARREST, a fibrin sealant patch for use as an adjunct to surgical hemostasis. With the approval of this supplement, the indication will be as follows:

> EVARREST™ is a fibrin sealant patch indicated for use with manual compression as an adjunct to hemostasis for control of bleeding during adult liver surgery and soft tissue bleeding during open retroperitoneal, intra-abdominal, pelvic, and non-cardiac thoracic surgery in adults when control of bleeding by standard surgical methods of hemostasis (e.g., suture, ligature, cautery) is ineffective or impractical.
>
> **Limitations for Use:**
> - Cannot be used in place of sutures or other forms of mechanical ligation in the treatment of major arterial or venous bleeding.

2. Background

EVARREST is a Fibrin Pad (FP) consisting of a sterile bio-absorbable flexible matrix and a coating of two biological components. The matrix consists of polyglactin 910 (PG910) filaments (b) (4) backing fabric of Oxidized Regenerated Cellulose (ORC). The biological components are Human Thrombin and Human Fibrinogen. EVARREST was licensed on December 5, 2012, as an adjunct to hemostasis during soft tissue surgery.

3. Chemistry Manufacturing and Controls (CMC)

See STN125392/0.

4. Nonclinical Pharmacology/Toxicology

In swine and rodent models, topically applied EVARREST was absorbed at approximately 8 weeks after application, with < 10% of the remaining material degrading exponentially over time. The biological components of EVARREST are degraded by fibrinolysis and phagocytosis, similarly to endogenous fibrin. As absorption progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated.

5. Clinical Pharmacology

There were no clinical pharmacology studies in this submission.

6. Clinical/ Statistical

a) Clinical Program

Efficacy data to support the expanded indication is from non-IND clinical study 400-10-001; safety data is based on study 400-10-001 and data from clinical study BIOS-13-005, conducted under IND 15628.

Non-IND Study 400-10-001

This non-IND study was conducted to obtain product approval from the European Medicines Agency (EMA).

This study was a randomized (1:1), active-controlled superiority study that compared EVARREST to local standard-of-care (SoC) in controlling surgical bleeding in hepatic parenchyma for which standard methods of achieving hemostasis were ineffective, impractical or inappropriate. The study was conducted in the UK, Germany, The Netherlands, Australia, and New Zealand. There were 104 subjects screened, with 84 subjects randomized to EVARREST (40 subjects) or SoC (44 subjects). The study included 104 subjects of median age 65 years (range 31 to 82 years); 58.7% of the subjects were male; 95.2% were White/Caucasian; 1.9% were Asian; 1% were Black; median body mass index was 27 kg/m2 (range: 15 to 43 kg/m2). Demographic characteristics were balanced across the treatment groups. The first subject at each clinical site was not randomized, but was treated with EVARREST to allow the surgeon to gain experience with the use of the product; this is referred to as the "Run-In" phase of the study, and this accounts for the difference of 20 subjects between the 104 screened and enrolled subjects versus 84 randomized subjects.

A Target Bleeding Site (TBS) in the liver parenchyma identified as the first actively bleeding site that continued to bleed after 30 seconds of manual compression was tried. The randomization was stratified based on whether the liver parenchyma was classified as Normal or Abnormal i.e.identified as cirrhotic, steatotic, or other [described as "fibrosis grade I"; "mottles as a consequence of previous surgical intervention and chemotherapy and liver hypertrophy"; "jaundiced"; "fatty"; "necrotic"; or "CACH (chemotherapie-associated steatohepatitis)"].

The EVARREST Fibrin Pad (4 x 4 inches) was cut to size based on the dimensions of the TBS wound site and applied to the wound. The SoC control arm was based on local practice. SoC was initiated with continuous firm manual compression with or without gauze or sponge and with or without a topical absorbable hemostat.

The primary endpoint was hemostasis at 4 minutes, with no re-bleeding at the TBS prior to wound closure. The following table shows the results for the primary endpoint:

Study 400-10-001:
Primary Efficacy Endpoint Results (ITT Set)

Classification of Hepatic Parenchyma	EVARREST	Standard of Care	p-value	Treatment Difference
All	33/40 (82.5%)	13/44 (29.5%)	<0.0001	53.0%
Normal	23/28 (82.1%)	11/33 (33.3%)	0.0001	48.8%
Abnormal	10/12 (83.3%)	2/11 (18.2%)	0.0009	65.2%

Subject 13-204 should have been randomized to EVARREST but was treated with SoC. This subject is analyzed in the EVARREST group in the ITT Set and in the SoC group in the Safety Set.
Source: STN125392/33 Study 400-10-001 clinical report page 62 of 146

Study BIOS-13-005

This study was ongoing at the time of submission of STN125392/33; the final study report was submitted on December 19, 2014, in STN125392/33.1. The study was conducted at 16 centers in the U.S., UK, Australia, and New Zealand.

Study BIOS-13-005 was a randomized, controlled, superiority study in adults to evaluate the effectiveness of EVARREST compared with standard of care (SoC) methods utilized to control bleeding in hepatic parenchyma for which standard methods of achieving hemostasis are ineffective or impractical. The study design closely comparable to the design of study 400-10-001, except eligible subjects were stratified based on the type of hepatic resection at the Target Bleeding Site (anatomic versus non-anatomic) and were randomized on a 1:1 basis, EVARREST vs. SoC control. As classified by the International Hepato-Pancreato-Biliary Association, anatomic resection was defined as resection of the neoplasms together with the portal vein related to the neoplasm and the corresponding hepatic territory; non-anatomic resection was defined as resection of a lesion without regard to segmental, section or lobar anatomy[1]. The stratification by the hepatic resection type was selected due to the potential difference in intra-operative hemostatic effectiveness between the resection types. This stratification was also required by the FDA. There were 104 subjects randomized (1:1) to EVARREST or SoC. Sixty-one percent of the subjects were male; 85.3% were White/Caucasian; 9.8% were Black; 2.0% were Asian; 3% were Hispanic. Median body mass index was 27 kg/m2 (range: 15 to 43 kg/m2). Demographic characteristics were balanced across the treatment groups.

The primary endpoint was hemostasis at 4 minutes, with no re-bleeding at the TBS prior to wound closure. The following table shows the results for the primary endpoint:

[1] Strasberg SM, Belghiti J, Clavin P-A et al. *HPB (Oxford)* **2**:333-239 (2000)

Study BIOS-13-005:
Primary Endpoint Results (ITT Set)

Type of Hepatic Resection	EVARREST	Standard of Care	p-value	Treatment Difference
All	(48/50) 96.0%	(24/52) 46.2%	<.0001	49.8%
Anatomic	(24/25) 96.0%	(13/23) 56.5%	0.0012*	39.5%
Non-Anatomic	(24/25) 96.0%	(11/29) 37.9%	<.0001*	58.1%

Source: STN125392/33.1 Clinical Report study BIOS-13-005, page 62 of 146

b) Pediatrics

The Pediatric Study Plan was agreed to by the Pediatric Research Committee on January 22, 2015. Pediatric studies in the age range 1 month to 17 years have been deferred. Studies in neonates (less than 1 month of age) have been waived because the applicant states the dimensions of the EVARREST fibrin pad may not be safe for use in the small bleeding surfaces of neonates undergoing liver surgery.

7. Safety

Non-IND Study 400-10-001

There were 462 adverse events (AEs) in 56 of the 59 subjects in the EVARREST arm, 16 of which were serious adverse events (SAEs); and 449 AEs in 42 of the 45 subjects in the SoC arm, 13 of which were SAEs. [The safety database is larger than the efficacy database because it includes 20 subjects who were "run-in" subjects who received EVARREST for the purpose of surgeon training.] There were no deaths. These AEs are further categorized in the following table:

Study 400-10-001:
Number of Subjects Experiencing any AE, SAE, Severe Adverse Event, Event Requiring Treatment or Related Event (Safety Set)

	EVARREST (N = 59)	Standard of Care (N = 45)
Total number of AEs	462	449
Total number of SAEs	23	13
Number (%) of subjects with at least one in the following categories:		
AE	56 (94.9%)	43 (95.6%)

SAE	16 (27.1%)	10 (22.2%)
Severe AE	10 (16.9%)	7 (15.6%)
Related or possibly related AE	3 (5.1%)	0 (0.0%)
Deaths	0 (0.0%)	0 (0.0%)

Source: STN125392/33 Study 400-10-001 clinical report page 83 of 146

The most frequently reported AEs were in the Gastrointestinal Disorders System Organ Class (SOC), as may be expected for a liver surgery study. The AEs anemia, nausea, constipation, vomiting, pain, pyrexia, hypokalemia, and hypotension were reported for more than 20% of subjects in the EVARREST arm. AEs in the EVARREST arm for which there were more than a 5% difference above the corresponding number of subjects in the SoC arm included dyspepsia (3 subjects), liver function test abnormal (3 subjects), hypoglycemia (3 subjects), hypomagnesemia (9 subjects), and anxiety (8 subjects). These excess AEs did not appear to be related to EVARREST, and it should be noted that the EVARREST safety database includes the 20 subjects treated in the practice "run-in" period (see above).

The SAEs are shown by SOC in section 6.1.12.4 of the clinical review memo and in the following table. The SAEs were balanced between the study arms, and appeared to be related to the underlying medical condition – liver surgery, and not the study agent. There were three SAEs that investigators judged to be possibly related to EVARREST; one subject experienced "post-operative bleeding", one subject experienced "intra-abdominal bleed with serosanguinous blood in drains", and one subject experienced "abdominal collection". Based on the nature of these three adverse events, the investigators may have judged them to be "related" based on inadequate therapeutic effect.

Frequency of SAEs by System Organ Class (Safety Set) Number (%) of Subjects Experiencing Event

System Organ Class	**EVARREST (N=59)**	**SoC (N = 45)**	**Total (N=104)**
Cardiac Disorders	4 (6.8%)	0 (0.0%)	4 (3.8%)
Gastrointestinal Disorders	5 (8.5%)	7 (15.6%)	12 (11.5%)
General Disorders & Administration Site Conditions	3 (5.1%)	0 (0.0%)	3 (2.9%)
Hepatobiliary Disorders	2 (3.4%)	1 (2.2%)	3 (2.9%)
Injury, Poisoning and Procedural Complications	4 (6.8%)	3 (6.7%)	7 (6.7%)

Respiratory, Thoracic and Mediastinal Disorders	3 (5.1%)	1 (2.2%)	4 (3.8%)
Vascular Disorders	0 (0.0%)	1 (2.2%)	1 (1.0%)

Source: STN125392/33 clinical report page 90 of 146

There were 4 AEs in 3 subjects in the EVARREST arm related to bleeding or thrombosis (two hematoma infections, 2 hematomas); there was one such AE in the SoC arm. These thrombosis/bleeding AEs were infrequent, and the sample size did not permit statistical evaluation of these low rates; however, these coagulopathic AEs did not appear to this reviewer to be related to the study agents, but to the underlying medical conditions of liver dysfunction and liver surgery.

Study BIOS-13-005

There were 409 adverse events in the EVARREST arm (N=50) and 430 adverse events in the SoC arm (N=52). Adverse events occurring in more than 20% of subjects in the EVARREST arm were nausea, constipation, hypotension, vomiting, pyrexia, hypokalemia, hypomagnesemia, and hypophosphatemia; all were non-serious.

SAEs

There were 43 SAEs experienced by 28 subjects (12 of 50 EVARREST; 16 of 52 SoC), including two deaths not related to the study agents (subjects 44101 in the EVARREST arm and 45103 in the SoC arm). EVARREST subject 44101 was a 62 year old male with a history of liver cirrhosis, hepatocellular carcinoma, renal cell carcinoma, obesity, type 2 diabetes mellitus, and hemochromatosis, who underwent exploratory laparotomy and left lateral hepatic segmentectomy with biopsy of a right hepatic lobe lesion. In the week following surgery, he experienced worsening renal failure with dialysis, pneumonia, and prolonged coagulation times (PT and aPTT). His death on day 8 after surgery was attributed to liver failure, with complication from the surgical procedure.

The SAEs are shown in the following table by SOC:

Study BIOS-13-005 Serious Adverse Events

System organ class	EVARREST N = 50	Standard of Care N = 52	Total N = 102
Blood and lymphatic system disorder	0 (0.0%)	1 (1.9%)	1 (1.0%)
Cardiac disorders	0 (0.0%)	2 (3.8%)	2 (2.0%)
Gastrointestinal	3 (6.0%)	5 (9.6%)	8 (7.8%)

System organ class	EVARREST N = 50	Standard of Care N = 52	Total N = 102
disorders			
Hepatobiliary disorders	1 (2.0%)	0 (0.0%)	1 (1.0%)
Infections and infestations	6 (12.0%)	7 (13.5%)	13 (12.7%)
Injury, poisoning and procedural complications	3 (6.0%)	3 (5.8%)	6 (5.9%)
Metabolism and nutrition disorders	1 (2.0%)	0 (0.0%)	1 (1.0%)
Psychiatric disorders	0 (0.0%)	1 (1.9%)	1 (1.0%)
Renal and urinary disorders	2 (4.0%)	3 (5.8%)	5 (4.9%)
Respiratory, thoracic and mediastinal disorders	1 (2.0%)	1 (1.9%)	2 (2.0%)
Vascular disorders	1 (2.0%)	0 (0.0%)	1 (1.0%)

Source: STN125392/33.1 Clinical Report Table 14.3.1.4, page 71 in Tables

There was one serious adverse event that was judged by the investigator to be possibly related to EVARREST. Subject 4403, a 62 year old female, underwent extended right hepatectomy with a resection of the extrahepatic biliary tree and Roux-en-Y heptico-jejunostomy. Two weeks after surgery she experienced abdominal fluid collection that was confirmed to be an abdominal abcess, and a relationship to EVARREST use could not be excluded.

Post-procedural bile leak was observed in one subject. This adverse event is important for fibrin sealant products in liver surgery because fibrin sealant products are reported to be compromised by bile, likely resulting in this adverse event. It is important to note that use of fibrin sealant in the EVARREST fibrin pad format may not be sufficient to prevent this complication. Additional studies would be informative.

Overall Safety Summary

There does not appear to be a safety signal in the safety data.

8. Advisory Committee Meeting

There was no presentation to the Blood Products Advisory Committee because there were no questions needing to be addressed by it.

9. Other Relevant Regulatory Issues

Fibrin sealant products for use as an adjunct to surgical hemostasis are given a specific indication based on the type of surgery studied. After the submission of clinical data from three or four types of surgery (e.g., soft tissue, solid organ, and vascular) covering a broad range of surgical bleeding sites, an applicant may request a general surgery indication, as an adjunct to hemostasis.

In STN125392/33, the applicant requested an additional indication for use as an adjunct to hemostasis for (b) (4) and indication not previously granted. CBER decided to limit the indication to "adult liver surgery" in keeping with the practice of basing the indication on the type of surgery studied.

10. Labeling

No major issues

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

This supplement may be approved.

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b) Risk/ Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Liver surgery creates large areas of parenchymal bleeding that must be addressed before surgical closure.	• EVARREST has demonstrated safety and efficacy for use as an adjunct to hemostasis in liver surgery.
Current Treatment Options	• There are several fibrin sealant products available for use as an adjunct to	• There is no unmet medical need because the clinical studies have not demonstrated a more significant clinical benefit from the use of EVARREST compared to

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	hemostasis in various surgical settings.	that of other adjunct to hemostasis products.
Clinical Benefit	• The indication for use as an adjunct to hemostasis in adult liver surgery is supported by the results of two clinical studies: the non-IND study 400-10-001 (84 subjects, 40 randomized to EVARREST) and the IND study BIOS-13-005 (102 subjects, 50 randomized to EVARREST). • Fibrin sealant products, when used as adjuncts to hemostasis, have not been able to demonstrate a traditional clinical benefit based on mortality or morbidity endpoints. For this reason, CBER decided to accept the surrogate endpoints of time-to-hemostasis or percent of subjects achieving hemostasis at a defined time point as acceptable primary endpoints for licensure. • Perhaps the major	• EVARREST has demonstrated clinical benefit for use as an adjunct to hemostasis in adult liver surgery, according to the surrogate endpoint percent of subjects achieving hemostasis at 4 minutes.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	benefit from the licensure of these products has been the decreased use of the surgical practice of “home brew” fibrin sealants made from fresh frozen plasma and licensed thrombin. These “home brew” products are thought to have a greater risk compared licensed fibrin sealant products that are validated to be virally safe.	
Risk	• EVARREST contains human thrombin and human fibrinogen, and therefore, there is a theoretical risk for perturbation of the coagulation system. • The absorbable matrix pad delivery system is novel, and therefore, potential effects on immunogenicity have not be fully evaluated.	• All the evidence indicates that the risk associated with the use of EVARREST as an adjunct to hemostasis is minor. There is no evidence of an increased risk for thrombogenicity or increased immunogenicity, however, continued surveillance for these events is advisable.
Risk Management	• Potential for perturbation of the coagulation system (e.g. thrombogenicity)	• Routine pharmacovigillance should address the concern for potential perturbation of the coagulation system. The Prescribing Information includes the contraindication:

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• Potential for adverse events because of possibly increased immunogenicity.	*Do not apply EVARREST intravascularly.* *Intravascular application of EVARREST may result in life-threatening thromboembolic events.* In addition, the following contraindication is intended to prevent the use of EVARREST in situations shown in non-clinical studies to present a potential risk for thromboembolism: *Do not use EVARREST to treat bleeding from large defects in visible arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency or where there would be persistent exposure of EVARREST to blood flow and/or pressure during absorption of the product.* • Routine pharmacovigilance should address the concern for potential for adverse events because of possibly increased immunogenicity. 1. Contraindication to not use in individuals known to have anaphylactic or severe systemic reaction to human blood products. 2. Statement under Warnings and Precautions that: *All blood products may in rare cases cause anaphylactic reactions. No adverse events of this type were reported during the conduct of the EVARREST clinical trials.*

c) Recommendation for Postmarketing Risk Management Activities

The applicant’s proposed risk management activities, as shown in the above table, are acceptable.

d) Recommendation for Postmarketing Activities

The safety of this indication will be monitored by routine pharmacovigilance.