Summary Basis for Regulatory Action

Date:	September 26, 2016
From:	Laurence Landow, MD
BLA/ STN#:	STN 125392/163
Applicant Name:	Ethicon, Inc.
Date of Submission:	December 18, 2015
PDUFA Goal Date:	October 17, 2016
Proprietary Name/ Established Name:	EVARREST/Fibrin Sealant Patch
Indication:	Indicated for use with manual compression as an adjunct to hemostasis in adult patients undergoing surgery, when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.
Recommended Action:	Approval

Signatory Authorities Action:

Offices Signatory Authority: Howard Chazin, MD, MBA, Acting Director
Division of Hematology Clinical Review, Office of Blood Research and 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	Laurence Landow, MD
Clinical Pharmacology Review	Iftekhar Mahmood, PhD
Statistical Review	Min (Annie) Lin, PhD
CMC Review	Natalya Ananyeva, PhD
Pharmacology/ Toxicology Review	La'Nissa Brown-Baker, PhD
Bioresearch Monitoring Review	Colonius King
Epidemiologic Review	Faith Barash, MD
Establishment Inspection Report	N/A
Advisory Committee Transcript	N/A

1. Introduction

Efficacy supplement STN 125392/163 is intended to support an expanded indication for EVARREST as a general adjunct to hemostasis in adult patients undergoing surgery when control of mild to moderate bleeding by conventional surgical techniques such as suture, ligature, and cautery is ineffective or impractical.

EVARREST (Fibrin Sealant Patch) is a sterile, bio-absorbable combination product comprised of two biological components - human plasma-derived fibrinogen and thrombin - coated onto a flexible composite patch consisting of an oxidized regenerated cellulose (ORC) layer underlying a layer of polyglactin 910 (PG910) non-woven fibers. In rodent and swine animal models, EVARREST is gradually absorbed by the body over an approximately 8 week period. Units of EVARREST used in the clinical trial were 10.2 x 10.2 cm (4 x 4 inches) in size.

2. Background

Fibrin Sealant products are an external source of thrombin and fibrinogen, the components required to form a clot. TachoSil is an equine collagen patch coated with human thrombin and human fibrinogen. FDA approved EVARREST as an adjunct to hemostasis for soft tissue (open retroperitoneal, intra-abdominal, pelvic and noncardiac thoracic) bleeding on December 5, 2012, and for solid organ (liver, spleen, kidney) bleeding on March 26, 2015.

3. Chemistry Manufacturing and Controls (CMC)

Not applicable.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology

Not applicable.

6. Clinical/ Statistical

a) Clinical Program

Two clinical study reports are included in the current submission.

Study 400-12-005

Study 400-12-005 was a randomized, single-blind, controlled (standard of care, SoC),[1] single-center, postmarketing safety study for use of EVARREST in subjects (N=150; EVARREST: N=75; SoC: N=75) undergoing soft tissue bleeding from a targeted bleeding site (TBS).[2] Soft tissue types included intra-abdominal, retroperitoneal, pelvic and noncardiac thoracic tissues but excluded parenchymal, vascular, gastrointestinal, bone or genitourinary tissue. Once the TBS was identified, the subject was randomized into the

[1] SoC in postmarketing study 400-12-005 was defined as manual compression (MC) ± topical absorbable hemostat (TAH) or any other adjunctive hemostasis technique deemed by the surgeon to be standard of care. Only one SoC subject (subject 10245) received MC alone.

[2] TBS was defined as an actively bleeding site identified in soft tissue where conventional hemostatic methods of control were ineffective or impractical and an adjunct was required for hemostasis.

study. Assigned treatment (EVARREST or SoC) was initiated along with 3 minutes of continuous firm mechanical compression (MC). Subjects were followed up to Day 30 (+/- 14 days) after discharge. The primary endpoint, a safety endpoint, was adverse events of special interest (AESI) over 30 days post-treatment and included (*a*) thromboembolic events (TEE), (*b*) post-operative rebleeding events specifically related to the TBS and (*c*) increased blood fibrinogen levels. In addition, ease of use data were collected using the Hemostasis Device Physician Ease of Use Questionnaire (EUQ-19). The results of this study are presented in, Section 7 Safety.

Study BIOS-13-004

Study BIOS-13-004 was a multicenter, multinational, randomized, single-blind, controlled (TachoSil) phase 3 study evaluating the safety and effectiveness of EVARREST as an adjunct to hemostasis in subjects (N=156; EVARREST: N=75; TachoSil: N=81) during thoracic aortic surgery. The primary endpoint in BIOS-13-004 was hemostasis at the TBS[3] at 3 minutes following treatment application and with no TBS rebleeding requiring treatment at any time prior to initiation of chest wall closure. Hemostasis was defined as no detectable bleeding at the TBS. Secondary endpoints included (*a*) hemostasis at the TBS at 6 and at 10 minutes following treatment application with no re-bleeding requiring treatment at the TBS prior to initiation of final chest wall closure, (*b*) incidence of rebleeding requiring treatment after initial establishment of TBS hemostasis for 3 minutes, and (*c*) incidence of adverse events (AE). Safety variables were collected beginning from time of randomization until approximately 60 days after the procedure.

Table 1 shows that EVARREST was superior to TachoSil in controlling bleeding at the TBS, with a success rate of 75% (57/76 Subjects) compared with 45% (36/80 Subjects) for subjects treated with TachoSil, i.e., a 30% absolute effect size. Median time to achieve hemostasis was 3 minutes in the EVARREST group (range: 3.0 to 88.3 minutes)[4] and 6 minutes in the TachoSil group (range: 3.0 – 145.0 minutes).

Table 1. Subjects Achieving Hemostasis at 3 Minutes Following Treatment Application, With No Re-Bleeding Up Until Chest Wall Closure

EVARREST	TachoSil	p-value	Treatment Difference
57/76 (75.0%)	36/80 (45.0%)	0.0001	30.0%

Additional Studies Reviewed

Study 400-12-002, a phase 2 study previously reviewed by FDA, was a randomized, dual-controlled (TachoSil or SoC),[5] study in subjects (N=42; EVARREST: N=13; TachoSil: N=18; SoC: N=11) undergoing cardiovascular surgery, i.e., aortic graft surgery in

[3] The TBS was defined as the first accessible aortic graft anastomotic site with mild to moderate suture line bleeding site requiring adjunctive treatment following 30 seconds of MC.

[4] Three minutes was the earliest point at which hemostasis could be assessed because the protocol required MC for 3 minutes after treatment application.

[5] SoC was defined in 400-12-002 as a composite of techniques and methods typically used by the surgeon to control bleeding when conventional methods (i.e., suture, ligation, cautery) are ineffective or impractical.

association with cardiopulmonary bypass. Following identification of a TBS (aortic graft suture line) that did not respond to 30 seconds of manual compression, subjects received EVARREST or one of the controls (1:1:1) accompanied by continuous firm manual compression. The primary efficacy endpoint was success in achieving hemostasis within 3 minutes following treatment application, with no re-bleeding at the TBS any time prior to chest wall closure. Only AEs or SAEs of special interest, such as TEE, post-operative bleeding at the treatment site, and increased fibrinogen were collected and reported.

The success rate for EVARREST subjects was 92.3% (12/13 subjects) *versus* 33.3% (6/18 subjects) for TachoSil subjects and 45.5% (5/11 subjects) for SoC subjects. The success ratio was 2.77 for EVARREST *versus* TachoSil (95% CI 1.53; 5.74) and 2.03 for EVARREST *versus* SoC (95% CI 1.18; 4.39).

7. SAFETY

Study 400-12-005

One fatality (SoC subject) occurred in Study 400-12-005. Both the number of SAEs (3 vs. 7) and the number of subjects who experienced SAEs (2 vs. 5) were higher in the SoC cohort. As depicted in Table 2, of the 6 AESIs reported in the EVARREST cohort, only a left axillary deep vein thrombosis (DVT) was possibly related to study product (AESIs in SoC subjects were not assessed for relationship to study product).

Table 2: AESIs in Study 400-12-005 (Safety Set)

Cohort	Subject ID	Adverse Event (POD #)	Relationship to Product	SAE
EVARREST	10144	Coagulopathic bleeding (3)	Unrelated	Yes
	10150	GI bleed (2)	Unrelated	
	10178	Left lower wall hematoma (14)	Unrelated	
	10224	Left axillary DVT (5)	Possibly-related	
	10247	Non-ST elevation MI (4)	Unrelated	Yes
		Left ventricular thrombus (4)	Unrelated	Yes
SoC	10118	Internal jugular vein (17) thrombosis	Unrelated	Yes
		Left axillary DVT (25)	Unrelated	Yes
	10124	Bleeding†	Unrelated	Yes
	10127	DVT (22)	Unrelated	Yes
	10180	DVT (2)	Unrelated	
	10185	Pulmonary embolus (15)	Unrelated	Yes
	10195	Pulmonary embolus (2)	Unrelated	Yes
	10208	Left peroneal DVT (11)	Unrelated	
	10243	DVT (11)	Unrelated	Yes
		Pulmonary embolus (11)	Unrelated	Yes

With respect to fibrinogen elevation, a statistically significant increase in mean fibrinogen levels (normal: 1.5 to 4.0 g/L) was observed from screening to discharge and from screening to 30-day follow-up in both treatment cohorts. As an acute phase reactant, these changes in fibrinogen, expected in a population undergoing major surgery were not clinically relevant because the magnitude of change (median) followed the same trajectory in the EVARREST and SoC cohorts, respectively, from Screening (3.30 and 3.25 g/L) to

Discharge (6.30 and 6.40 g/L) and from Screening to 30-day follow-up (4.68 and 5.39 g/L).

Table 3 summarizes safety data by subject (regardless of causality) and shows that fewer adverse events were associated with EVARREST than with SoC; however, caution is warranted in assessing these data due to small sample size.

Table 3: Number of Subjects in 400-12-005 Experiencing AEs or SAEs (Safety Set)

Variable	EVARREST N=75	SoC N=75
Total number of AEs	6	10
Total number of SAEs	3	7
Number (%) of Subjects with ≥1 in the following categories		
AE	5 (6.7%)	8 (10.7%)
SAE	2 (2.7%)	5 (6.7%)
Severe AE	0	2 (2.7%)
Possibly related to study product	1 (1.3%)	0
Possibly related to procedure	0	0
Death/Ongoing at death	0	1 (1.3%)
Rebleeding at the TBS†	1	1
Thromboembolic event	2 (2.7%)	7 (9.3%)
AE classified as anastomotic bleeding	3 (4.0%)	1 (1.3%)

Study BIOS-13-004

Table 4 summarizes safety data by subject (regardless of causality) and shows that safety profiles for EVARREST and SoC (TachoSil) were comparable.

Table 4: Number of Subjects in BIOS-13-004 Experiencing AEs or SAEs (Safety Set)

Variable	EVARREST N=75	SoC N=81
Total number of AEs	602	589
Total number of SAEs	69	59
Number (%) of Subjects with ≥1 in the following categories		
Death	4 (5.3%)	3 (3.7%)
SAEs	31 (41.3%)	34 (42.0%)
SAEs possibly related to study product*	3 (4.0%)	1 (1.2%)
Severe intensity AEs	17 (22.7%)	19 (23.5%)
AEs	73 (97.3%)	80 (98.8%)
AEs possibly related to procedure	68 (90.7%)	69 (85.2%)
TBS rebleeding AEs possibly related to the product	3 (4.0%)	2 (2.5%)
Thromboembolic AEs possibly related to the product	5 (6.7%)	3 (3.7%)
Deep sternal wound infection AEs possibly related to the product	0	0

*Applicant assessment performed for SAEs only

Study 400-12-002

Table 5 summarizes safety data by subject (regardless of causality) and shows that the safety profile of the EVARREST cohort was comparable to the comparators.

Table 5: Number of Subjects in 400-12-002 Experiencing AEs or SAEs (Safety Set)

Variable	EVARREST N=13	TachoSil N=18	SoC N=11
Total number of AEs	54	114	71
Total number of SAEs	6	17	15
Number (%) of Subjects with ≥1 in the following categories			
AE	11 (84.6)	18 (100)	11 (100)
SAE	3 (23.1)	10 (55.6)	6 (54.5)
Severe AE	0	3 (16.7)	4 (36.4)
Possibly related to study product	2 (15.4)	2 (11.1)	0
Possibly related to procedure	10 (76.9)	18 (100)	9 (81.8)
Rebleeding event	0	2 (11.1)	0
Thromboembolic event	0	2 (11.1)	2 (18.2)

Integrated Overview of Safety

A total of 8 randomized, controlled, clinical studies (including the 3 studies mentioned above) enrolling 653 subjects were conducted to support the general adjunct to hemostasis indication. Three types of surgical procedures were represented: soft tissue surgery (N=232: abdominal, pelvic, retroperitoneal, noncardiac thoracic), solid organ surgery (N=223: hepatic, partial nephrectomy) and cardiovascular surgery (N=198: thoracic aortic surgery).

Table 6 summarizes safety data by subject for the 8 studies and shows that the safety profile of EVARREST was comparable to control.

Table 6: Summary of Adverse Events (Integrated Safety Set)

	EVARREST N=381(%)	Control N=272 (%)
Total no. of AEs	2857	2244
Total no. of SAEs	215	171
Number (%) of Subjects with ≥1 in the following categories		
AE	358 (94.0)	262 (96.3)
SAE	118 (31.0)	101 (37.1)
Severe AE	76 (19.9)	57 (21.0)
Rebleeding AE	11 (2.9)	10 (3.7)
Death	15 (3.9)	8 (2.9)
Thrombotic events	18 (4.7)	12 (4.4)

8. Advisory Committee Meeting

No meeting was held.

9. Other Relevant Regulatory Issues

Not applicable.

10. Labeling

There were no disagreements with the applicant over changes to the submitted labeling recommended by FDA.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

I recommend an approval action be taken for this BLA supplement.

b) Risk/ Benefit Assessment

The risk-benefit profile is favorable; the risks associated with use of EVARREST in adults are out-weighed by the hemostatic benefit and is comparable to other adjuncts.

c) Recommendation for Postmarketing Risk Management Activities

Routine postmarketing surveillance is recommended.

d) Recommendation for Postmarketing Activities

There are no recommended postmarketing requirements or commitments for clinical purposes.