**Clinical Review Memorandum**

**DATE**:

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**SUBJECT**: supplemental BLA application (PAS) to fulfill the Pediatric Research Equity Act Post Marketing Requirement.

**PRODUCT:** EVARREST Fibrin Sealant Patch (Fibrin Pad)

**APPLICANT:** ETHICON, Inc.

**BLA:** 125392

**SUBMISSION DATE:** December 8, 2026

**PDUFA GOAL DATE:** October 8, 2026

**REVIEW COMPLETION:** **October 8, 2026**

**RECOMMENDATION:** Approval

## Executive Summary

The purpose of this memo is to review the proposed changes to the United States Package Insert (USPI) for EVARREST in this BLA efficacy supplement based on data from completed pediatric studies to fulfill PREA requirements.

EVARREST was originally approved in the United States (US) in 2012, based on data from four clinical studies (Study 400-07-002, Study 400-08-002, Study 400-10-001, FL-PN-001-IS) following response to a Complete Response (CR) letter. 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. 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.). 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 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 original BLA for EVARREST Fibrin Sealant Patch was submitted to the Agency on November 19, 2010. Following review of the submission, FDA issued a CR letter on September 19, 2011, based on: (a) insufficient clinical information to assure safety of EVARREST in the intended surgical population in light of adverse event (AE) of thrombosis(es) observed in the Phase 2 400-07-002 study, and (2) outstanding cGMP issues during inspection. The unfavorable safety trend against EVARREST was related to the imbalance in the pulmonary embolism (PE) reactions seen in the clinical trial. Of the five (5) subjects in the EVARREST treatment arm who experienced the PE, 2 subjects had the PE within 2 days of the surgical procedure, 1 subject had a “suspected” PE on the day of surgery with no computerized tomographic confirmation of the embolism, and the remaining 2 subjects experienced the PE at days 15 and 20 post surgery. Based on the EVARREST mechanism of action, FDA concluded that the PE adverse reactions seen within 2 days of the surgical procedure in the 2 subjects could plausibly have a causal relationship to treatment with EVARREST, and for the remaining subjects, other factors (radiographic evidence, temporal relationship, underlying malignancy, smoking history, diabetes, cardiovascular disease) were presumed as the likely cause of PE. Also, considering that most subjects included in the studies had underlying malignancies, FDA reviewed the surgical published literature for venous thromboembolism rate among the general population suffering from cancer. The reported background rate was within 3-5% and comparable to the overall incidence of the PE adverse reactions seen across all studies with use of EVARREST. For this original approval in 2012, FDA subsequently requested additional data from a future clinical study designed to monitor thrombotic events. Note, there was a second CR issued on 28 September 2012, citing issues with labeling. Ethicon incorporated all the FDA recommendations in the respective labeling and submitted the revised versions to the FDA as a response to the CR letter (received on 9 October 2012). The Applicant submitted additional data from a liver resection surgery study, as supplemental efficacy amendment, for which FDA issued an approval letter, dated March 26, 2015.

On December 8, 2025, Ethicon Inc (The Applicant), submitted efficacy supplement containing the final study report for the Pediatric Research Equity Act (PREA) Post Marketing Requirement (PMR) and draft updated package insert to include the pediatric indication and pediatric clinical data. An FDA-agreed PSP (IND 015098, BLA 125392 Post-Approval Requirement for EVARREST) required the deferred pediatric study under PREA (BIOS-16-001, n= 35 pediatric subjects treated with EVARREST), the results of which were to be integrated with the earlier European study (400-12-004, n= 20 pediatric subjects randomized to EVARREST and 20 pediatric subjects to the control, SURGICEL). Study 400-12-004 was an open-label, prospective, multi-center, randomized, active-controlled clinical study, and BIOS-16-001 was an open-label, prospective, multicenter, single-arm study. Both trials evaluated the safety and effectiveness of EVARREST as an adjunct to control mild or moderate bleeding in children from

1 month (≥28 days from birth) to less than 18 years of age, requiring non-emergent, open hepatic, abdominal, retroperitoneal, pelvic, or thoracic (non-cardiac) surgical procedures. Of note, with the exception of randomization, the study procedures for 400-12-004 and BIOS-16-001 were similar in regard to baseline demographics, types of surgeries.

For the current PAS, Applicant revised labeling for fulfillment of the PREA requirement by adding information regarding safety and efficacy of EVERREST from the two completed pediatric studies, under Pediatric Use in section 8, sub-section 8.4, as well as subsection 14.4, in addition to updating the safety, under Adverse Reactions, in section 6, and subsection 6.1. Additionally, FDA updated this older label to be consistent with the labels for Cell and Gene Therapy approved products. Sections were updated in the Limitations of Usage, dosage and administration (Section 2), Warnings and Precautions, Other minor editorial changes have been made to ensure consistency with labeling requirements and FDA guidance.

In the integrated analysis of these studies, a total of 55 subjects were treated with EVARREST, with at least 50% treated at hepatic parenchyma. Table 1 displays the efficacy analyses from these studies. The target bleeding site (TBS) was to be defined during the dissection related to the primary operative procedure, as the first actively bleeding site in the soft tissue or hepatic parenchyma that showed challenging mild or moderate bleeding for which conventional methods of bleeding control were ineffective or impractical and for which an alternative method of hemostasis was required. The TBS had to be accessible and amenable to manual compression, and it had to be a site where occlusion of the blood vessels of the bleeding tissue surface was required to achieve hemostasis, thus excluding large defects in large arteries or veins where the injured vascular wall required repair with maintenance of vessel patency. TBS was defined as mild bleeding, with a small area of capillary, arteriole or venule bleeding; Moderate Bleeding was defined as TBS with a larger area of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss, or a TBS with bleeding that is more pronounced than oozing, that could also come from a small artery or vein, but is not massive.

The Primary Endpoint was time to hemostasis (TTH), defined as the absolute time elapsed from randomization (for study 400-12-004) or from bleeding site identification (for study BIOS-16-001), to the last moment in time at which detectable bleeding at the TBS was observed. Note, in BIOS-16-001, there were 2 subjects (Subject (b) (6) and Subject (b) (6)) with a major protocol deviation concerning the study procedure, whereby the 4-minute hemostasis assessment was performed at 4 minutes after the EVARREST patch application, rather than at 4 minutes from TBS identification as was required by the protocol. This influenced the results for the primary endpoint of TTH in the FAS (for Subject (b) (6)) and Safety analysis set (for both subjects).

**Table 1: Efficacy Results**

| Characteristic | EVARREST 400-12-004 N=20 | EVARREST BIOS-16-001 N=35 | EVARREST Pooled N=55 | SURGICEL N=20 |
|---|---|---|---|---|
| Hemostatic success at **4 minutes** and no bleeding requiring treatment at the TBS any time prior to final fascial closure [1] | | | | |
| n | 20 | 31 | 51 | 20 |
| Yes | 16 (80.0%) | 24 (77.4%) | 40 (78.4%) | 12 (60.0%) |
| No | 4 (20.0%) | 7 (22.6%) | 11 (21.6%) | 8 (40.0%) |
| 95% CI | (56.34%, 94.27%) | (58.90%, 90.41%) | (64.68%, 88.71%) | (36.05%, 80.88%) |
| Hemostatic success at **10 minutes** and no bleeding requiring treatment at the TBS any time prior to final fascial closure [3] | | | | |
| | 20 | 31 | 51 | 20 |
| Yes | 19 (95.0%) | 29 (93.5%) | 48 (94.1%) | 18 (90.0%) |
| No | 1 (5.0%) | 2 (6.5%) | 3 (5.9%) | 2 (10.0%) |
| 95% CI | (75.13%, 99.87%) | (78.58%, 99.21%) | (83.76%, 98.77%) | (68.30%, 98.77%) |

† 400-12-004 Study was a randomized controlled study, with the active comparator SURGICEL
Summary statistics are based on subjects with non-missing data.
[1] Defined as the absolute time elapsed from randomization (for 400-12-004) or from TBS identification

In the Pooled EVARREST group, additional treatment involved manual compression in 8/10 subjects. One subject was re-treated with EVARREST following accidental dislodgement of the patch by the surgeon and hemostasis was again achieved. One subject received rescue treatment of additional surgical methods and an alternative hemostatic agent. In the SURGICEL group, there was 1/20 (5.0%) subjects with 1 AE assessed by the Investigator as a moderate, non-serious AE of Hemorrhage “Possibly related to SURGICEL;” a second SURGICEL-treated subject experienced re-bleeding at the TBS; this was a mild non-serious AE of Hemorrhage which the Investigator categorized as “not related to SURGICEL.”

Overall, the safety profile demonstrated in the pediatric clinical trials was favourable. Pooled safety data from the EVARREST group showed 42/55 (76.4%) subjects with at least one AE, and 13/55 (23.6%) subjects with at least one SAE (18 individual SAEs). None of the subjects experienced death or a thrombotic event. Summary of the AEs were reported as the following: bradycardia or tachycardia (43.6%); gastrointestinal disorders involving nausea/vomiting/abdominal pain (50.9%), infections (16.4%), and pyrexia (25.5%). In the SURGICEL group, 18/20 (90.0%) subjects reported at least one AE, and 5/20 (25.0%) with at least one SAE (16 individual SAEs). None of the subjects experienced death or a thrombotic event or. Summary of the AEs were reported as the following: bradycardia or tachycardia (45.0%), gastrointestinal disorders involving nausea/vomiting/abdominal pain (60.0%) infections (15.0%), and pyrexia (45.0%).

All AE reported in clinical trial patients (adults and pediatrics) treated with EVARREST (511 patients), occurred at a frequency of less than 1% of patients. AE reported as single occurrences were; abdominal abscess, intestinal ischaemia, localized intra-abdominal fluid collection, peripancreatic fluid collection, and pulmonary embolism. Additional events reported in >1 patient were: anastomotic hemorrhage (3 patients, 0.6%), blood fibrinogen increased (3 patients, 0.6%), deep vein thrombosis (2 patients, 0.4%), intra-abdominal hemorrhage (2 patients, 0.4%), operative hemorrhage (2 patients, 0.4%), pleural effusion (2 patients, 0.4%), and post procedural hemorrhage (2 patients, 0.4%). In the Control groups, adverse reactions reported as single occurrences were blood fibrinogen increased (0.4%, standard of care treatment), intra-abdominal hemorrhage (0.4%, oxidized regenerated cellulose), pleural effusion (0.4%, standard of care treatment), and rash (0.4%, TachoSil Fibrin Sealant Patch)

> *Reviewer Comment: These reported AEs related to gastrointestinal issues, cardiac abnormalities, infections, and electrolyte abnormalities, are not unique to the product EVARREST, but may be confounded due to the underlying surgery or complication(s) from surgery.*

During the review of this efficacy supplement, two information requests (IR) were sent to Applicant. The first IR requested Applicant provide a rationale to support the dosing in pediatric population. The second IR was sent to Applicant in response to FDA's discussions with PeRC regarding the lowest age to which the label can be expanded. During the PeRC meeting on July 7th, 2026. Applicant clarified,

> *Per the Agency's letter of 19 November 2012 (revised 29 November 2012), "the PeRC agreed with the Division to grant a deferral of pediatric studies and a waiver for the neonatal pediatric population (0—30 days). 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) section of the package insert." Accordingly, a partial waiver for EVARREST pediatric studies in neonates (from birth up to 1 month of age) in all surgical procedures was approved under section 505B(a)(4)(B) of the Pediatric Research Equity Act (BL 125392/163 Approval Letter of 07 October 2016)…There are differences in the plasma levels of some coagulation factors in neonates, infants, and children when compared to adults. However, reported serum concentrations of fibrinogen are essentially equal in each of these groups, without measurable differences in levels between different pediatric age brackets when compared to levels seen in adults. The availability of endogenous fibrinogen at a target bleeding site would therefore not be different in subjects of different ages, and therefore the ability of Human Fibrinogen and Human Thrombin to accelerate local clotting would be expected to be comparable.*

Several internal deliberations were held between clinical team, PeRC, and leadership. Neonatal hemostasis differs physiologically from that of older children and adults, and the age at which the coagulation system fully matures remains poorly defined. A key regulatory question for the current sBLA is whether available data are sufficient to support labeling down to patients

younger than 7 months, given that the sponsor's studies did not include this age group. This evidence gap was flagged as a central concern during PeRC review.

By comparison, VISTASEAL (BLA 125640/220) achieved labeling down to birth based on data from just 6 neonates. Other randomized controlled clinical trial evidence supports use of EVARREST in ECMO-focused neonatal population, demonstrating that fibrin sealant reduces bleeding and hemorrhage duration, and in a Phase III study (2024) of Evicel in pediatric patients (ages ~0.9–17 years) showing an acceptable safety profile with no thrombotic events — though both trials had limited enrollment of the youngest neonatal patients. Although Applicant provided data to support expansion to pediatric population from 1 month and older, FDA is exercising regulatory flexibility, after reanalyzing the previously submitted adult data to the original BLA (approval dated 2012), the two pediatric studies (submitted to Amendment 645), and based on the E11 guidance (https://www.fda.gov/media/161190/download), which was published in December 2024. The review team determined it is appropriate to extrapolate the efficacy and safety demonstrated in the studied population to pediatric patients younger than 1 month of age for the following reasons:

a. Neonatal hemostasis may be different than that of older children and adults; however, the exact age at which the coagulation system is considered fully established is not well characterized. Data in published literature evaluating fibrin sealant as a topical hemostatic agent in neonates undergoing ECMO, found that fibrin sealant significantly reduced the risk of bleeding, the volume of shed blood, and the duration of hemorrhage which is particularly useful in neonates with coagulopathy who failed standard surgical hemostasis. Overall, the response to treatment with EVARREST is expected to be similar across pediatric patients of different ages as the therapy is applied topically and there is no expected systemic absorption.
b. The product dosing is based on body surface area (BSA), including weight for ages 1 month and olde, and using BSA for dosing in neonates (<1 month) is feasible and appropriate.
c. Efficacy assessments were the same in the adult treated population as were in the evaluated pediatric population between 7 months of age and 15 years and the clinical outcomes assessed are similarly applicable to patients younger than 1 month of age.
d. No serious safety signals were identified in studied pediatric patients over 6 months old and adults. There is no expectation of different safety of the product as it is applied topically.

The following major changes were negotiated with the Applicant during review of this BLA supplement.

- Section on Indications and Usage was updated to expand indication to include adults and pediatric patients (all ages).
- Non-pooling of the two pediatric studies for safety and efficacy data, under Section 8.4 because the studies that fulfill PREA requirement were not of the same clinical design and the interpretation of the data is essentially different where there is no comparator arm (Study BIOS-16-001).

- Pediatric efficacy data presentation of hemostasis as proportion of patients achieving time to hemostasis at the pre-specified 4 minutes and 10 minutes.
- Sections on Adverse Reactions, under Section 6, and Clinical Trial Experience, under Section 14, needed updating of the post marketing clinical data.

**Conclusion**

EVARREST is a biological-device combination product made of two biological components (human plasma-derived fibrinogen and human plasma-derived thrombin) embedded in a flexible composite backing layer composed of cellulose (device). The mechanism of action of EVARREST is based on the interaction between the biological components, which follows the principles of physiological fibrin clot formation. EVARREST has received three separate approvals. In 2012, it was approved for soft tissue bleeding, specifically in open retroperitoneal, intra-abdominal, pelvic, and noncardiac thoracic procedures. In 2015, the approval was expanded to include liver surgery. In 2016, the approval was further expanded to include thoracic(b) (4) surgery and cardiovascular surgery.

In summary, in this BLA efficacy supplement, the Applicant provided evidence of safety and effectiveness for hemostasis in pediatric population (studied in ages 7 months to 15 years), fulfilling the PREA requirement for pediatric studies in 1 month to 17 years of age. Although the studied population included pediatric patients 7 month and older, the pathophysiology of bleeding/clotting, the clinical response to the local treatment with EVARREST, and the safety of the product administered locally are expected to be similar across all pediatric age groups undergoing surgical procedures. Therefore, it is scientifically reasonable to extrapolate efficacy and safety from pediatric patients (7 months and older) and adults to younger pediatric patients, down to birth.

**Recommended Regulatory Action:** Approval with agreed-upon changes to the USPI.

Concurrence and Signatures

| Name/Office | Title | Concurrence | Signature/Date |
|---|---|---|---|
| Anam Tariq, DO | Branch Chief<br>General Medicine Branch 4<br>DCEGM, OCE, OTP, CBER | Concurrence | ANAM TARIQ -S<br>Digitally signed by ANAM TARIQ -S<br>Date: 2026.10.08 17:02:01 -04'00' |
| Patroula Smpokou, MD | Director<br>DCEGM, OCE, OTP, CBER | Concurrence | PATROULA I. SMPOKOU -S<br>Digitally signed by PATROULA I. SMPOKOU -S<br>Date: 2026.10.08 17:09:19 -04'00' |