

**Mid-Cycle Review Memorandum:
Evarrest Fibrin Pad
OBE/DE Review for Pharmacovigilance Planning**

BLA STN 125392
Evarrest Fibrin Pad
Omrix

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Introduction

OBE/DE has completed a review of the pharmacovigilance plan for Biological Licensing Application STN 125392, **EVARREST** fibrin pad. The purpose of this review is to identify potential safety issues that may need to be addressed through post-market safety monitoring, studies, or other pharmacovigilance activities, should the product be approved.

Product Background

EVARREST Fibrin Pad is a yellow white bioabsorbable product made from a combination of a flexible matrix, coated with two human plasma derived proteins. The matrix component consists of an oxidized, regenerated cellulose backing, under a layer of polyglactin 910 non-woven fibers. This provides physical support for the biological components, imparts mechanical integrity and supports clot formation.

The biological components contain the biologically active ingredients Human Fibrinogen and Human Thrombin. On contact with a bleeding wound surface, the biological components hydrate and the fibrinogen-thrombin reactions initiate the clot formation in the usual cascade. The manufacturing procedures include processing steps designed to reduce the risk of viral transmission.

The non-active side of the matrix has an embossed wave pattern, to distinguish it from the active side.

EVARREST Fibrin Pad is indicated as an adjunct to hemostasis for soft tissue bleeding for **Mild to Moderate bleeding** during retroperitoneal, intra-abdominal, pelvic and non-cardiac thoracic surgery when control of bleeding by standard surgical techniques proves ineffective or impractical.

Contraindications include use in cases of severe bleeding from defects in large arteries or veins, where injury to vascular wall requires repair and maintenance of vessel patency. Persistent exposure of Fibrin Pad to blood flow and pressure during healing and absorption of the product is not advised. Intravascular application of Fibrin Pad may result in life-threatening thromboembolic events.

It is not advised to use in individuals who have had anaphylactic reactions to human blood products or other components of the Fibrin Pad. It is not advised for use in infected tissue.

The quantity to be applied is dependent on the size and location of the site to be treated. The pad should cover the entire target bleeding site, with overlap of 1 to 2 cm as necessary. Manual pressure should be applied for 3 minutes. The use of more than four 4 x 4 units, or the use in patients who have been previously exposed, has not been studied.

The pharmacology of Fibrin Pad has been studied in a number of animal models. . Fibrin Pad was evaluated in vascular repair models to evaluate usefulness in primary and permanent repair or large defects in large vessels. In this scenario, Fibrin Pad is exposed to persistent blood flow and high pulse pressure. In these models, early and late failures, pseudoaneurysms and emboli were observed. The conditions under which these were observed were beyond the intended indication.

Clinical Safety Data

A total of 125 subjects have been treated with Fibrin Pad during three completed clinical studies. Each subject was treated during a single surgical procedure. This population is referred to as the Total Safety Set.

Study # 400-07-002

Abdominal, pelvic, retroperitoneal, and non-cardiac thoracic surgery 111 subjects
A pivotal multicenter, prospective, randomized, controlled, study comparing Fibrin Pad to SURGICEL® in subjects undergoing non-emergent abdominal, retroperitoneal, pelvic, and thoracic surgery where a topical hemostat is indicated.

One hundred and forty one (141) subjects gave consent and were enrolled into the study. Ninety (90) subjects were included during the randomized phase of the study (60 FP; 30 SURGICEL) and an additional 51 nonrandomized subjects were treated with FP. Subjects were recruited at 11 centers in the US, each of which recruited between 1 and 32 subjects.

Phase of Study: Phase II

Study # FL-PN-001-IS

Partial nephrectomy

10 subjects

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One hundred and eleven subjects were treated with Fibrin Pad during a Phase II study to evaluate the efficacy and safety of Fibrin Pad used as an adjunct to hemostasis for mild and moderate soft tissue bleeding. Of these, 60 subjects were treated during the randomized phase of the study, and 51 were treated during a subsequent non-randomized phase in which all subjects received treatment with Fibrin Pad. This study was conducted in 11 US institutions.

Study FL-PN-001-IS was a phase I study during which Fibrin Pad was used as an adjunct to hemostasis in addition to conventional surgical methods.

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Study # 400-08-002

In addition, safety data are available for 69 subjects treated with either Fibrin Pad or Control during an **ongoing** soft tissue bleeding Phase II study conducted outside the US. Subjects were randomized in a 2:1 ratio to Fibrin Pad or Control, and therefore includes approximately 46 subjects treated with Fibrin Pad. This study aims to recruit between 90 and 180 randomized subjects from centers in the EU, Australia and New Zealand.

Post-market Experience

There is no post-market experience with this product, as it has not been marketed in any country.

Pediatric patients have not been included in studies with Fibrin Pad. A pediatric deferral is being sought with the intent of deferring assessment of pediatric safety until after the initial approval of Fibrin Pad.

Pharmacovigilance Planning

When a new product is marketed, the exposed population may differ from the population studied in pre-approval trials.

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket reporting requirements under FDA regulations) is sufficient for post-marketing risk assessment. As outlined in Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (<http://fda.gov/CDER/guidance/63590CC.htm>), FDA believes pharmacovigilance plans

may be appropriate when: 1) Serious safety risks have been identified pre- or post-approval, or 2) at risk populations have not been adequately studied. The pharmacovigilance plan is developed by a product's sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified safety risks.

Safety Assessment

Important Identified and Potential Risks

Theoretical potential risks identified prior to the clinical development program were:

- Rebleeding at the site of application
- Thrombotic Events
- Immunogenicity of the biological components
- Rare occurrence of severe anaphylaxis, especially if the preparation is applied repeatedly, or administered to patients with known hypersensitivity to the constituents of the product
- Antibodies to any components of the product may form. Adverse events that could be attributed to immunogenicity include allergic reactions or anaphylactic reactions.
- Medicinal products prepared from human blood or plasma may carry a risk of transmitting infectious agents such as viruses, and could theoretically transmit Creutzfeldt-Jakob disease. This risk has been minimized by screening plasma donors for prior exposure and by inactivating and removing infectious agents during the manufacturing process.
- Some viruses, such as Parvovirus B19 are particularly difficult to remove or inactivate. Parvovirus B19 seriously affects pregnant women, immunocompromised individuals, or individuals with hemolytic anemia.
- The Matrix may swell during use. If used in, around, or in proximity to foramina in bone or areas of bony confine, this presents a potential risk of nerve compression.
- The matrix components should be used with caution in contaminated areas of the body, and in common with other topical hemostatic devices, should not be used in the presence of active infection.

These potential risks were specifically evaluated during **Study 400-07-002**. Evaluation of similar events is being conducted in **ongoing Study 400-08-002**.

Immunogenicity of the biological components was assessed by assaying plasma samples collected at baseline and 4 to 6 weeks and 8 to 10 weeks after treatment.

The antibody response to Human Thrombin and Fibrinogen was evaluated in patients treated with Fibrin Pad or Surgicel during study 400-07-002. Samples from 99 subjects treated with Fibrin Pad and 22 subjects treated with Surgicel were analyzed. 2% of the Fibrin Pad treated group had a slight increase in antibody response to Human Thrombin. At the four week post-treatment mark, neither group had abnormal coagulation parameters. No response to Human Fibrinogen was detectable. There is no data available about re-exposure. Experience with the biological and Matrix components of

Fibrin Pad does not suggest any potential for overdose. Nevertheless, this has been included as a potential risk.

Fibrin Pad has not been determined to carry potential for misuse for illegal purposes.

Adverse Events Identified as Potentially Related to Fibrin Pad during Clinical Studies

The safety analysis sets is comprised of 141 subjects, of whom 111 were treated with FP (the “FP All” group) and 30 with SURGICEL. The incidence of subjects with at least one AE was comparable between treatment groups: 94.6% (105/111 subjects) in the FP All group and 90% (27/30 subjects) in the SURGICEL group.

The incidence of subjects who experienced at least one SAE was lower in the FP group than the SURGICEL group. The incidence rates were 36.0% (40/111 subjects) in the FP All group and 50.0% (15/30 subjects) in the SURGICEL group. Medical, surgical or other action was taken for AEs for 93.7% (104/111 subjects) in the FP All group and 83.3% (25/30 subjects) in SURGICEL group. AEs that were related or possibly related to study product were experienced by 3/111 subjects (2.7%) in the FP All group and 2/30 subjects (6.7%) in the SURGICEL group. One subject randomized to FP experienced an SAE of intraluminal GI Hemorrhage and one non-randomized FP subject experienced an SAE of operative hemorrhage; neither event occurred at the treated TBS site but both were assessed by the investigators as possibly related to treatment. One additional non-randomized FP subject experienced 4 events that were assessed as possibly related to treatment (Ascites, Infected Pancreatic Fluid Collection, Suspected Pulmonary Embolism and Deep Vein Thrombosis). Imaging studies failed to confirm the DVT and PE diagnoses.

A total of 796 AEs occurred in subjects treated with FP, with 105/111 (94.6%) experiencing at least one event. Forty out of 111 subjects (36.0%) experienced at least one SAE, 27/111 subjects (24.3%) experienced at least one severe AE and 104/111 subjects (93.7%) experienced at least one AE that required medical, surgical or other intervention.

By comparison, among subjects receiving SURGICEL, there was a total of 250 AEs affecting 27/30 subjects (90.0%). Fifteen out of 30 subjects (50.0%) experienced at least one SAE, 9/30 subjects (30.0%) experienced at least one severe AE and 25/30 subjects (83.3%) experienced at least one AE that required medical, surgical or other intervention.

AEs that were considered to be possibly or probably related to study treatment occurred in 3/111 subjects (2.7%) in the FP All group and 2/30 subjects (6.7%) in the SURGICEL group.

The most frequently occurring type of AE by SOC was Metabolism and Nutritional Disorders and within this class, hypomagnesia was most frequently reported event, occurring in 59/141 (41.8%) of subjects overall. Hyperglycemia, hypokalemia and hypophosphatemia all occurred in more than 20% of subjects.

Eight AEs in 5 subjects were assessed as being potentially treatment related; 6 events occurred in 3/111 subjects in the FP All group and two events occurred in 2/30 subjects in the SURGICEL group.

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Since non-clinical testing indicated a potential risk for pseudoaneurysm and bleeding if Fibrin Pad is used to repair defects in large arteries or veins, the prescribing information for Fibrin Pad contains the following contraindications:

- Fibrin Pad should not be used to treat severe bleeding from large defects in large arteries or veins where injury requires repair and maintenance of vessel patency. Do not use in situations that would result in persistent exposure to blood flow and pressure during healing and absorption of the product.
- Fibrin Pad should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

Major Safety Concerns

Ongoing Safety Concerns

Important Identified Risks

Non-clinical data indicate that Fibrin Pad should **not** be used to treat severe bleeding from large defects in large arteries or veins where injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of **EVARREST** to blood flow and pressure during healing and absorption of the product.

Important Potential Risks

The following important potential risks have been identified for Fibrin Pad:

- Potential risk of thrombotic events
- **Do not apply EVARREST intravascularly.** Intravascular applications of EVARREST may result in life-threatening thromboembolic events.
- EVARREST should not be used to treat severe bleeding from large arteries or veins.
- Development of pseudoaneurysm has occurred in these situations.
- Rare occurrence of hypersensitivity/allergic reactions
- Isolated occurrence of severe anaphylaxis, especially if preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product
- Incorrect application could represent a potential risk of lack of efficacy(includes application of the inactive side to bleeding surfaces, application of insufficient pads to adequately cover the bleeding site, or incomplete contact of the product to tissue, wrinkles or folds or displacement of the Fibrin Pad during the surgical procedure.)
- As with all therapeutic proteins, there is the potential for immunogenicity
- There is the possibility of transmitting infectious agents
- Overdose is a possible, but unlikely, risk

Important Missing Information

Uncommon or rare events may be missed due to the small size of the population in the clinical trials. There is no data available about re-exposure to the product.

Pharmacovigilance Plan

Routine Pharmacovigilance Practices

Omrix Biopharmaceuticals Ltd. operates a routine pharmacovigilance system in accordance with current international regulations and guidelines.

No actions are planned beyond the routine pharmacovigilance for any of the potential risks. The prescribing information warns about the identified and potential risks in the contraindications and warnings and precautions sections

Omrix Biopharmaceuticals will ensure that all aspects of the pharmacovigilance system are maintained and executed in accordance with the international regulations and local market commitments. This will be accomplished via direct execution of activities and contracting of service providers. Where services are outsourced, there will be agreements in place to outline roles and responsibilities.

- --(b)(4)-- Will provide case processing/submission of ICSR (Individual case safety reports) and PSUR (Periodic safety update reports) compilation, literature reviews and drug safety database management.
- Ethicon, Inc. (a Johnson & Johnson Company), will provide clinical affairs, medical affairs, pharmacovigilance, sales and marketing distribution, and customer interface support.
- An initial safety report may be sent to OMRIX or directly to (b)(4) pharmacovigilance service provider from any source, such as physicians, pharmacists, literature or non-medical sources. If the report is sent directly to OMRIX, it will be immediately forwarded to ----(b)(4)---- acknowledges receipt, assesses and classifies the report, checks for validity, accuracy, completeness and seriousness. The report is then assigned a number and entered into the global safety database. If expedited reporting is required, a MedWatch report is prepared and sent to the appropriate regulatory authorities within statutory timelines.
- Cases may be closed after the appropriate number of follow-up attempts have been made (at least two at two week intervals for serious cases), and re-opened if additional information is received.
- All relevant case reports and information concerning the safety of the product is described in the PSUR and Annual safety reports.
- Quality Assurance at OMRIX is responsible for the overall management of the -----(b)(4)----- Quality Assurance program. (b)(4) has a dedicated quality and process training function at the global and regional levels, which control operating guidelines and ensure the pharmacovigilance functions and procedures are harmonized.

Non-Routine Plans

The need for post-marketing data generation will be discussed with FDA.

Post-market commitments to complete ongoing study # 400-08-002.

Establish registry for data on thromboembolic events and immunogenicity,

Consider pediatric trial after use in adult population has been shown to be safe.

Pharmacovigilance Planning Assessment and Recommendations

- The sponsor has submitted a pharmacovigilance plan following ICH E2E PVP guidance (<http://fda.gov/CDER/guidance/63590CC.htm>)
- Complete Study # **400-08-002**, and submit results as they are available. This may be considered a post-market commitment, should the product be approved.
- Consider conducting a Phase III study with a greater number of enrollees, pending analysis of the data from Study # 400-08-002. The studies presented are of small study size, the composition of the enrollees is not gender or race balanced. The subjects are quite ill, with increased incidence of overall adverse events. Should analysis of newly submitted data prove to be inadequate, a well-designed confirmatory Phase III study may be considered.
- Establish and maintain a patient registry for monitoring potential adverse events, with attention to thromboembolic events and immunogenicity.
- As part of the PVP, the sponsor should submit all reports of thrombotic events, regardless of labeling or seriousness.
- Should the product be approved, perform a Phase IV study for evaluation of re-exposure of product.

Conclusion

The Sponsor has submitted a Pharmacovigilance Plan according to ICH E2E guidance. An extremely high number of adverse events were noted in both the Fibrin Pad group and the control group, likely due to the population enrolled. The enrollees had a high rate of obesity, malignancy, and other co-morbidities.

Available data indicate the potential for a serious risk of thrombotic events. The studies performed had a small number of subjects, most of whom had multiple co-morbidities to place them at increased risk for thromboembolic events. For this reason, please conduct a Phase IV study to evaluate the risk of thromboembolic events. There is concern about the randomization protocol, and the exclusion criteria used.

Additionally, concern exists that should the product be approved, there is a possibility that it will be used off label for a variety of indications.

For this reason, a confirmatory study should be considered that has a greater number of subjects and includes the following:

- Gender-balanced and Race-balanced enrollment of subjects with and without co-morbidities
- Scheduled monitoring of adverse events, specifically including signs and symptoms of thrombotic adverse events
- Scheduled monitoring for immunogenicity using a validated assay that can detect antibodies to the components of **EVARREST**.

In addition to routine PV monitoring, the sponsor should consider submission of all reports of thrombotic events, regardless of investigator determination of relatedness, labeling or seriousness, and a patient registry.

Letter-ready Comments

- You have submitted a pharmacovigilance plan following ICH E2E PVP guidance (<http://fda.gov/CDER/guidance/63590CC.htm>).
- Complete Study # **400-08-002**, and submit results as they are available.
- Please conduct a phase IV study to evaluate re-exposure and a patient registry in addition to routine PV monitoring; to further assess potential safety risks from **EVARREST, including thromboembolic events**, should the submission be approved.
- Submit any thromboembolic adverse events reported from any source as expedited adverse event reports, whether or not they are considered labeled events or related to the product, and whether or not the product was being used for its labeled indication.