

**Final 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 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 -----
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----- . 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 the original three completed clinical studies. Each subject was treated during a single surgical procedure. This population is referred to as the Total Safety Set. **This does not include Study #400-08-002.**

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

A Phase II Randomized, Controlled, Superiority Study Evaluating the Fibrin Pad Versus Standard of Care Treatment in Controlling Severe Soft Tissue Bleeding During Abdominal, Retroperitoneal, Pelvic, and Thoracic Surgery

This study involved 15 investigators in 4 countries.

The primary objective of this study was to evaluate the safety and hemostatic effectiveness of the Fibrin Pad (FP) versus standard of care treatment (SoC) in controlling challenging severe soft tissue bleeding during abdominal, pelvic, retroperitoneal, and (non-cardiac) thoracic surgery

Safety data are available for 91 subjects treated with either Fibrin Pad or Control during a 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 59 subjects treated with Fibrin Pad and 32 subjects treated with “standard of care”. Subjects were recruited at 15 centers in the UK, Germany, New Zealand and Australia, each of which recruited between 1 and 20 subjects

All 91 subjects enrolled in the study received the allocated study treatment during surgery and 76/91 (83.5%) completed the study as planned.

The study population was not representative of a general surgery population, undergoing usual procedures for benign indications.

Phase of Study: II

Safety Results for Study # 400-08-002

The rates of Adverse Events were comparable in both groups, with AE's noted in 98.3% of the Fibrin Pad group and 100% of the SoC group. This is difficult to evaluate clinically, as essentially all of the participants experienced at least one adverse event.

22% of the Fibrin Pad subjects experienced a severe adverse event, and 28% of the SoC subjects experienced an adverse event. Medical, surgical or other actions taken for adverse events were actually higher in the Fibrin Pad group (93.3%) as compared to the SoC group (90.6%). The most frequently occurring AE was gastrointestinal, with nausea and constipation being the most frequent. It is not clearly documented what the interventions were.

The most concerning adverse events include the incidence of thromboembolic events and abscess formation. The Fibrin Pad remains in situ until reabsorption. This may increase risk of thrombosis or abscess.

AEs that were considered to be related or possibly related to study product were experienced by 5/59 subjects (8.5%) in the FP group and 1/32 subjects (3.1%) in the SoC group. These events included clinically significant increases in fibrinogen levels evaluated as possibly related to treatment in 3/59 subjects (5.1%) treated with FP and 1/32 subjects (3.1%) treated with SoC. However, in two of the three cases treated with FP, fibrinogen was also elevated at screening. Fibrinogen is known to be an acute phase reactant protein. The relationship to treatment and the clinical significance of these results is unclear given the known effect of surgery on fibrinogen levels and the variability in individual responses.

Clinically significant increases in fibrinogen levels were reported as possibly related to treatment in 3/59 subjects (5.1%) treated with FP and 1/32 subjects (3.1%) treated with SoC; all four subjects were treated in the same centre. Elevated fibrinogen levels may raise the concern for development of coagulopathy, particularly upon re-exposure.

Two thrombotic events occurred in the FP treatment group (2/59, 3.4%) and one in the SoC group (1/32; 3.1%). One subject treated with FP developed a thrombosis of the R subclavian vein during insertion of a peripherally inserted central catheter and in one subject in the SoC group, who had an inferior vena cava (IVC) filter inserted prior to surgery, an adverse event of IVC filter thrombosis was reported. Neither event was considered to be related either to the study treatment or to the surgical procedure.

An additional subject in the FP group suffered a fatal AE of massive gastric aspiration due to ileus caused by ischemic bowel. The possibility that ischemia was caused by a thrombotic event cannot be ruled out.

Seven deaths occurred during the study, 4 in the FP group (6.8%) and 3 in the SoC group (9.4%).

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 conducted in **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 in Study 400-07-002.

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.

In Study 400-08-002, elevations of fibrinogen levels were noted. The sponsor reports that the fibrinogen levels returned to normal by discharge. The clinical importance of this is unclear.

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

This is data from Study 400-07-002

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.

During Study 400-07-002, six AE's in 3/111 subjects were identified as being possibly related to study treatment. One subject developed GI hemorrhage, thought to be possibly related. Subject had undergone a Whipple pancreaticoduodenectomy and subsequently developed massive GI bleed. This was determined to not have been from the target bleeding site, but causal relationship could not be ruled out. One subject developed ascites, infected pancreatic fluid, deep vein thrombosis and suspected pulmonary embolism, thought to be possibly related. DVT and PE were based on clinical assessment at the bedside, but Duplex scanning of the lower extremities and CT scan were negative for DVT and PE. One subject developed Operative hemorrhage, thought to be possibly related. The principal investigator confirmed that the event was related to the surgical procedure and occurred at a site other than the TBS. However, it was reported as a potential TBS rebleed.

Thrombotic and thromboembolic Adverse Events

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Evaluation of the safety data showed a random distribution of AE's and SAE's, with the exception of a temporal cluster of thrombotic/thromboembolic events observed during the non-randomized phase of Study 400-07-002 in subjects treated with a single lot of Fibrin Pad.

Potential thrombosis-related events in the Safety Set were reported in 8/111 subjects (7.2%; 6/111 5.4% VTE and 2/111 1.8% arterial) treated with FP, as compared to 2/30 (6.7%: all VTE) of subjects treated with SURGICEL

In the randomized Study 400-08-002, potential thrombosis related serious adverse events were seen in 2/69 subjects (2.9%).

Immunogenicity

Assessment of the relative immunogenicity (ELISA -----(b)(4)-----) of the biologically active components in Fibrin Pad revealed no relevant differences in antigenicity. There is still the possibility of allergic or anaphylactic reactions to the components of the Fibrin Pad.

Other

Potential for Off-Label Use

Off-Label Use could potentially include:

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The potential for Off-Label Use is considered to be high.

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.

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
- Potential risk of abscess formation
- **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. There is no data available on re-exposure.
- 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.

The possibility of a post-marketing requirement has not been ruled out.

Establish registry for data on thromboembolic events and immunogenicity,

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

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 malignancy and multiple co-morbidities.

The study 400-08-002 fails to add further safety information to the existing data from study 400-07-002. There is still a very high level of adverse events in both groups. Because of the high level of background “noise”, it is not possible to confidently identify a true safety signal. Should this product be approved, it is likely to be used in a general surgery population. Conduct a **well-designed Phase III** study with a study population more representative of a general population, should re-submission be considered.

Available data indicate the potential for a serious risk of thrombotic events. The studies performed had a small number of subjects most of whom were at increased risk for thromboembolic events, due to the increased risk from both malignancy and lengthy surgery. There is also risk of infection, abscess formation and other adverse events.

Re-bleeding is recorded as a non-serious adverse event. This reviewer considers the possibility that re-bleeding may be an efficacy issue. Elevated Fibrinogen levels raise a concern, even if the levels return to normal at the time of discharge. It is unclear whether this will present a problem with coagulopathy or thrombosis if there is re-exposure. We anticipate that if this product were to be approved, it would be used frequently for a variety of indications, and probably a number of off label uses.

There is no information available regarding re-exposure or the possibility of coagulopathy or thrombosis in light of increased fibrinogen levels detected.

For these reasons, should approval be granted, a Phase IV study will be a Post-Marketing Requirement. If approval is not granted and resubmission is considered, a well designed confirmatory Phase III study should be conducted that has a greater number of subjects and includes the following:

- Gender-balanced and Race-balanced enrollment of subjects with and without co-morbidities. Enrollees should be subjects with and without malignancy and undergoing a variety of surgical procedures, to be representative of the likely use.
- Scheduled monitoring of adverse events, specifically including signs and symptoms of thrombotic adverse events and abscess.
- Scheduled monitoring for immunogenicity using a validated assay that can detect antibodies to the components of **EVARREST**.

Pharmacovigilance Planning Assessment and Recommendations

- The sponsor has submitted a pharmacovigilance plan following ICH E2E PVP guidance (<http://fda.gov/CDER/guidance/63590CC.htm>)
- Should approval be granted, a Phase IV study with a greater number of enrollees representative of the general population will be required. This request is due to the 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, and have multiple co-morbidities. The subjects experienced an increased incidence of overall adverse events. Additionally, there are a number of protocol violations.
- Should approval not be granted and resubmission is considered, conduct a **well-designed confirmatory Phase III** study with a study population more representative of a general surgery population. The patient population selected was such that it is difficult to identify a true safety signal in the background of numerous adverse events.

- As part of the PVP, the sponsor should submit all reports of thrombotic events, regardless of labeling or seriousness and all reports of abscess formation.
- Should the product be approved, a Phase IV study for evaluation of thrombosis, abscess and re-exposure to product will be required.
- The language used in the submission is vague. The terms “severe” adverse event versus “serious” adverse event are unclear, as is the term “challenging” severe bleeding.

Letter-ready Comments

- You have submitted a pharmacovigilance plan following ICH E2E PVP guidance (<http://fda.gov/CDER/guidance/63590CC.htm>).
- Study # **400-07-002** and # **400-08-002** fail to provide adequate safety information to provide certainty about the safety of the product, should it be used in a general surgery population.
- Should approval be granted based on Study # **400-07-002** and # **400-08-002**, a **Phase IV** Observational Pharmacoepidemiologic study to evaluate thromboembolic events and re-exposure will be required. Section 901 of the FDA Amendments Act (FDAAA) section 505(o) authorizes the FDA to require postmarketing studies or clinical trials at the time of approval, or after approval. FDAAA 505(o)(3)(B) states that studies or clinical trials may be required for one of three purposes:
 - a. To assess a known serious risk related to the use of the drug;
 - b. To assess signals of serious risk related to the use of the drug; or
 - c. To identify an unexpected serious risk when available data indicate the potential for a serious risk.
- Should re-application be considered, based on a **well designed Phase III** study to evaluate risks of thrombo-embolic events, abscess and re-exposure, the study should be of a representative population for the likely uses of the product. If the data provided allows assessment of the risks identified above, a patient registry and routine pharmacovigilance may be sufficient, obviating the need for a postmarketing requirement (PMR).
- 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. Please also submit any adverse events related to abscess formation or infection similarly. Routine monitoring and reporting of adverse events should be conducted, including submitting 15-day expedited reports for serious, unlabeled adverse events and Periodic Safety Update Reports, quarterly for the first three years after licensure and yearly thereafter, as required under 21 CFR 600.80.