ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

EVARREST Sealant Matrix

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1:
Human Fibrinogen 8.1 mg/cm^2

Component 2
Human Thrombin 40 IU/cm^2

Excipient(s) with known effect:
Contains up to 3.0 mmol (68.8 mg) sodium per sealant matrix.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sealant Matrix

EVARREST is a white-to-yellow bio-absorbable combination product made from a flexible composite Matrix, coated with Human Fibrinogen and Human Thrombin. The active side of the sealant matrix is powdery, and the non-active side has an embossed wave pattern.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment in adult surgery where standard surgical techniques are insufficient (see section 5.1):
- for improvement of haemostasis.

4.2 Posology and method of administration

The use of EVARREST is restricted to experienced surgeons.

Posology
The amount of EVARREST to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

The quantity of EVARREST to be applied depends upon the area and location of the bleeding area to be treated. EVARREST should be applied so it extends approximately 1 to 2 cm beyond the margins of the target bleeding area. It can be cut to the size and shape required to fit the size of the bleeding area.

Bleeding areas larger than those which can be covered by a single unit of EVARREST have not been investigated in clinical studies. EVARREST should only be used in a single layer, with an overlap of approximately 1 to 2 cm onto non-bleeding tissue or an adjacent EVARREST sealant matrix.

Multiple bleeding sites may be treated simultaneously. In total, no more than the equivalent of two 10.2 cm x 10.2 cm units or four 5.1 cm x 10.2 cm units should remain in the body as there is only limited long-term experience with larger quantities. The use of more than four 10.2 cm x 10.2 cm units or eight 5.1 cm x 10.2 cm units, or the use in patients that have been previously exposed to EVARREST, has not been studied.

If haemostasis is not reached with one application of EVARREST, re-treatment may be administered.

Paediatric population
The safety and efficacy of EVARREST in children from birth to 18 years has not yet been established. No data are available.

Method of administration

For epilesional use only.

For instructions on preparation of the medicinal product before administration, see section 6.6. The product should only be administered according to the instructions recommended for this product (see section 6.6).

4.3 Contraindications

- EVARREST must not be applied intravascularly.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- EVARREST must not be used to treat severe bleeding from large defects in large arteries or veins where the injured vascular wall requires repair with maintenance of vessel patency and which would result in persistent exposure of EVARREST to blood flow and/or pressure during healing and absorption of the product.
- EVARREST must not be used in closed spaces (e.g., in, around, or in proximity to foramina in bone or areas of bony confine) since swelling may cause nerve or blood vessel compression.
- EVARREST must not be used in the presence of active infection or in contaminated areas of the body because infection may occur.

4.4 Special warnings and precautions for use

For epilesional use only. Do not apply intravascularly

Life-threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

As with any protein containing product, allergic-type hypersensitivity reactions are possible. Signs of hypersensitivity reactions include hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the product should be removed immediately and other hemostatic agent or methods should be used.
In case of shock, standard medical treatment for shock should be implemented.

EVARREST should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

Applications for which adequate data are not available
Adequate data are not available to support the use of this product in neurosurgery or application through a flexible endoscope for treatment of bleeding, in vascular surgery, or in gastrointestinal anastomoses.

As with any implantable product, foreign body reactions may occur.

EVARREST should only be used in a single layer, with an overlap of approximately 1 to 2 cm onto non-bleeding tissue, to assist with adherence to the wound site. The size of EVARREST should be limited to what is necessary for haemostasis.

EVARREST contains up to 3.0 mmol (68.8 mg) sodium per sealant matrix. To be taken into consideration by patients on a controlled sodium diet.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped virus hepatitis A virus (HAV). The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or abnormal erythropoiesis (e.g., haemolytic anaemia).

It is strongly recommended that every time EVARREST is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Similar to comparable products or thrombin solutions, the product may be denatured after exposure to solutions containing alcohol, iodine, or heavy metals (e.g., antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.

4.6 Fertility, pregnancy and lactation

The safety of fibrin sealants/haemostatics for use in human pregnancy or during breast-feeding has not been established in controlled clinical trials. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation, and peri- and post-natal development.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/haemostatic products. In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to constituents of the product.

Antibodies against components of fibrin sealant/haemostatic products may occur rarely.

Thromboembolic complications may occur if the preparation is unintentionally applied intravascularly (see section 4.4).

For safety with respect to transmissible agents, see section 4.4.

Adverse Reactions

The safety data for EVARREST reflect the types of post-operative complication generally related to the surgical settings in which the trials were conducted and the underlying disease of the patients. In clinical trials, the most frequently reported adverse reactions were haemorrhage and increased fibrinogen, and the most serious adverse reactions were aspiration, pulmonary embolism, and haemorrhage.

EVARREST was used to treat soft tissue bleeding during retroperitoneal, intra-abdominal, pelvic, or thoracic surgery, suture hole bleeding during cardiovascular surgery, and parenchymal bleeding during hepatic or renal surgery across all clinical trials involving 381 subjects treated with EVARREST and 272 control subjects. Of the enrolled subjects, 4.7% of EVARREST treated subjects (18 subjects out of 381) and 2.6% of control subjects (7 subjects out of 272) experienced one or more adverse reactions.

A post-marketing safety study enrolling 150 subjects was conducted using EVARREST. It was a prospective, randomised, controlled single-centre study observing the clinical utility of EVARREST against Standard of Care (SoC) in soft tissue bleeding during intra-abdominal, retroperitoneal, pelvic and non-cardiac thoracic surgery. Standard of Care was manual compression (MC) with or without a topical absorbable haemostat (TAH) or any other adjunctive haemostasis technique that was deemed by the surgeon to be his/her standard of care.

Study subjects were followed post-operatively through discharge and at Day 30 (+/-14 days) post discharge. The incidence of thromboembolic events, the incidence of post-operative bleeding events specifically related to the target bleeding site and the incidence of increased blood fibrinogen levels were assessed and recorded up to the 30 days follow-up period.

One (1/75) adverse reaction of deep vein thrombosis was reported in the EVARREST group.

Immunogenicity was evaluated in soft tissue clinical studies by testing blood samples collected at baseline, 4 to 6 weeks, and 8 to 10 weeks post-surgery for antibodies to human thrombin and fibrinogen by enzyme-linked immunosorbent assays. Three subjects out of 145 (~2%) in the group treated with EVARREST showed an increase in the titre of anti-thrombin antibodies after treatment. Two subjects out of 145 (~1%) in the group treated with EVARREST showed a transient increase in fibrinogen antibody titres, with titre levels back at background levels at the 8 to 10 week time point.

Tabulated list of adverse reactions

Data from eight clinical trials with EVARREST have been pooled into an integrated dataset and the frequencies of occurrence described in the table below originate from this integrated dataset. In the integrated analyses, 381 patients were treated with EVARREST and 272 patients were treated with control treatment.

All adverse reactions reported during the clinical trials occurred at a frequency of less than 1% (uncommon). Most adverse reactions were reported as single events: intra-abdominal haemorrhage, abdominal distension, anaemia, thoracic cavity drainage, pleural effusion, abdominal abscess, ascites, deep vein thrombosis, localized intra-abdominal fluid collection, operative haemorrhage, ischaemic bowel and pulmonary embolism, except blood fibrinogen increased (3 events, 0.8%), anastomotic haemorrhage (3 events, 0.8%), and post procedural haemorrhage (2 events, 0.5%)

The following categories are used to rank the adverse reactions by frequency of occurrence: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); and very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1Summary of Adverse Reactions to EVARREST

MedDRA System Organ Class	**Preferred Term**	**Frequency**
Vascular disorders	Deep vein thrombosis	Uncommon
Respiratory, thoracic and mediastinal disorders	Aspiration Pleural effusion Pulmonary embolism	Uncommon Uncommon Uncommon
Gastrointestinal disorders	Abdominal distension Ascites Haemorrhage ● Gastrointestinal haemorrhage ● Intra-abdominal haemorrhage Localised intra-abdominal fluid collection Peripancreatic fluid collection	Uncommon Uncommon Uncommon Uncommon Uncommon
Investigations	Blood fibrinogen increased	Uncommon
Injury, poisoning and procedural complications	Post-procedural haemorrhage Operative Haemorrhage Anastomotic Haemorrhage	Uncommon Uncommon Uncommon

Description of selected adverse reactions

Pulmonary embolism

Blood clots, including those clots that may travel in blood vessels to other parts of the body, particularly the lungs (pulmonary embolus) may occur after any major surgery. In clinical trials of EVARREST no difference has been observed between EVARREST and control groups with regard to the incidence of thrombotic events, currently suggesting no increased risk with EVARREST use. Due to the nature of surgical procedures and the physiological response to surgical trauma all surgical subjects are at risk for occurrence of thromboembolism.

Deep vein thrombosis

The overall incidence of deep vein thrombosis observed during clinical trials was consistent with published data and does not suggest an increased risk for thrombotic events in EVARREST-treated subjects, although from the available data, this risk cannot be completely ruled out.

Anti-thrombin antibodies

Three subjects out of 145 (~2%) in a clinical trial group treated with EVARREST showed an increase in the titre of anti-thrombin antibodies after treatment. None of the patients in any treatment group had a significant change in antibody titre to thrombin or fibrinogen.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, local haemostatics, ATC code: B02BC30

Mechanism of Action

EVARREST contains Human Fibrinogen and Human Thrombin as a dried coating on the surface of an absorbable composite Matrix. In contact with physiological fluids, e.g., blood, lymph, or physiological saline, the components of the coating are activated, and the reaction of fibrinogen and thrombin initiates the last phase of physiological blood coagulation. Fibrinogen is converted into fibrin monomers which spontaneously polymerise to form a fibrin clot that holds the Matrix firmly to the wound surface. The fibrin is then cross-linked by endogenous Factor XIII, creating a firm, mechanically stable fibrin network with good adhesive properties.

The composite Matrix is composed of polyglactin 910 and oxidized regenerated cellulose, a commonly used haemostat. The Matrix provides physical support and a large surface area for the biological components, imparts inherent mechanical integrity to the product and supports clot formation. The clot formation of EVARREST is integrated with the Matrix; it forms a mechanical barrier to bleeding and reinforces the wound site. Natural healing occurs while the fibrin degrades and the product is absorbed by the body; absorption is considered to take approximately 8 weeks, as demonstrated in rodent and swine animal models.

Clinical efficacy and safety

Clinical studies demonstrating haemostasis in mild or moderate soft tissue bleeding were conducted in a total of 141 subjects (111 treated with EVARREST and 30 with control) undergoing abdominal, retroperitoneal, pelvic, and (non-cardiac) thoracic surgery. A further trial in 91 patients undergoing abdominal, retroperitoneal, pelvic, and (non-cardiac) thoracic surgery (59 treated with EVARREST and 32 with control) demonstrated haemostasis in severe soft tissue bleeding. Two clinical studies in 206 patients undergoing hepatic surgery (110 treated with EVARREST and 96 with control) demonstrated haemostatic efficacy in persistent parenchymal bleeding.

A prospective randomised controlled clinical study was conducted enrolling 156 subjects (76 EVARREST, 80 haemostatic fleece) demonstrating the safety and haemostatic effectiveness of EVARREST as an adjunct to controlling bleeding during cardiovascular surgery.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with EVARREST in one or more subsets of the paediatric population for the treatment of haemorrhage resulting from a surgical procedure (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

EVARREST is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Studies have been conducted in rabbits to evaluate the absorption and elimination of thrombin when applied to the cut surface of the liver resulting from partial hepatectomy. Using ^{125}I-thrombin it was shown that a slow absorption of biologically inactive peptides resulting from the breakdown of thrombin occurred, reaching a C_{max} in the plasma after 6-8 hours. At the C_{max}, the plasma concentration represented only 1 to 2% of the applied dose.

Fibrin sealants/haemostatics are metabolised in the same way as endogenous fibrin, by fibrinolysis and phagocytosis.

After the biologic components have been absorbed, the Matrix components (polyglactin 910 and oxidized regenerated cellulose) absorb completely. In animal studies EVARREST was absorbed by 56 days when used at the anticipated clinical dose.

5.3 Preclinical safety data

The haemostatic efficacy of EVARREST was demonstrated in a number of animal models assessing time to haemostasis and post-treatment blood loss, among other endpoints.

Non-clinical data on the Matrix component reveal no special hazard for humans based on studies of cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, material-mediated pyrogenicity, subchronic toxicity, genotoxicity, implantation, and hemocompatibility.

A 90-day study in rats to evaluate subchronic systemic toxicity and immunogenicity of EVARREST after subcutaneous implantation found no signs of toxic effects and no evidence of increased immunogenicity relative to fibrin sealant products.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Composite Matrix (Polyglactin 910 and oxidised regenerated cellulose) 20 mg/cm2
Arginine hydrochloride
Glycine
Sodium chloride
Sodium citrate
Calcium chloride
Human albumin
Mannitol
Sodium acetate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Once the foil sachet is opened, EVARREST can remain in the sterile field to be available for use throughout the procedure.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

10.2 cm x 10.2 cm sealant matrix in a tray (polyester). The tray is in a sachet (polyester laminated aluminium foil) with a seal. Pack size of 1, 10.2 cm x 10.2 cm sealant matrix.

5.1 cm x 10.2 cm sealant matrix in a tray (polyester). The tray is in a sachet (polyester laminated aluminum foil) with a seal. Pack size of 2, 5.1 cm x 10.2 cm sealant matrices.

6.6 Special precautions for disposal and other handling

The instructions for use are also described in the in the healthcare professional's package leaflet part.

- EVARREST comes ready to use in sterile packages and must be handled using sterile technique in aseptic conditions. Discard damaged packages.
- To open the product, remove the foil sachet from the carton, carefully peel open the foil sachet avoiding contact with the inside of the foil or the white sterile tray containing EVARREST.
- Remove the white sterile tray from the pouch and place onto the sterile field.
- Hold the tray securely in the palm of the hand, ensuring that the side with the holes is facing upwards, and use the tabs on the side of the tray to remove the top of the tray with the other hand.
- The lower portion of the tray contains EVARREST with the active side facing downwards. The active side is powdery in appearance. The non-active side has an embossed wave pattern.
- Keep EVARREST dry after opening. The product can remain in the sterile field to be available for use throughout the procedure. EVARREST does not stick to gloves, forceps, or surgical instruments.

Application of EVARREST

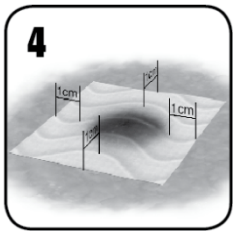
EVARREST is to be applied with approximately 3 minutes of firm manual compression.

1. Using sterile scissors, carefully cut EVARREST to the size and shape as necessary to fit and maintain contact with the bleeding area with an overlap of approximately 1 to 2 cm. Keep the powdery white-to-yellow colour active side of EVARREST facing down while in the tray.

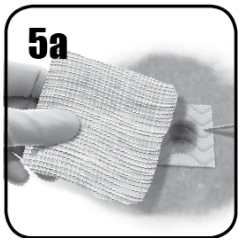
2. Remove excess blood or fluid from the site of application if required to improve visibility. The bleeding source should be clearly identified, and it must be ensured that EVARREST is applied directly onto the bleeding source by covering it completely. EVARREST can be used in an actively bleeding field.

3. Apply the active side of EVARREST to the bleeding area, allowing full contact with the tissue. The product is activated upon contact with fluid, and adheres and conforms to tissue.

4. Apply an appropriately sized piece of EVARREST to adequately cover the entire bleeding area, with an overlap of approximately 1 to 2 cm onto non-bleeding tissue, to assist with adherence to the wound site.

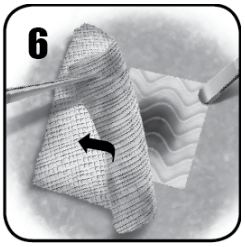


5a) Hold dry or moist surgical gauze or laparotomy pads over EVARREST to achieve full contact with the bleeding surface.



5b) To ensure haemostasis, immediately apply manual compression over the entire surface of EVARREST (including the area of overlap) sufficient to stem all bleeding. Maintain compression for approximately 3 minutes, to control the bleeding.

6. Gently remove surgical gauze or laparotomy pads from the application site, without disrupting or dislodging EVARREST or the clot. Inspect EVARREST to verify that haemostasis has been achieved and to ensure that there is no crimping over the bleeding area. If not satisfied with the placement, remove EVARREST and use a new EVARREST sealant matrix. EVARREST will remain in place and adhere to the tissue, and is absorbable.



7. The application site should be monitored intraoperatively to verify that haemostasis is maintained.

Re-Treatment

- Re-treatment may be required if there are folds, creases, or crimps in the EVARREST sealant matrix. If not satisfied with the placement of EVARREST, remove the used EVARREST

sealant matrix and repeat the application procedure above with a new EVARREST sealant matrix.

- If bleeding is due to insufficient coverage of the bleeding area, additional EVARREST sealant matrices may be applied. Apply in a single layer; ensure that the edges overlap (by approximately 1 to 2 cm) with the existing EVARREST sealant matrix.

- If bleeding is due to incomplete adherence to the tissue (where bleeding persists from under the dressing), remove EVARREST sealant matrix and use a new EVARREST sealant matrix.

- If bleeding still occurs during or after the specified duration of compression, remove the used EVARREST sealant matrix and inspect the bleeding site. If no other primary haemostatic measures (i.e., standard surgical techniques) appear to be required, repeat the application procedure above with a new EVARREST sealant matrix.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

Omrix Biopharmaceuticals N.V.
Leonardo Da Vincilaan 15
1831 Diegem
Belgium
Telephone: +32 2 746 30 00
Telefax: + 32 2 746 30 01

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/868/001
EU/1/13/868/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 September 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Human Fibrinogen and Human Thrombin:
Omrix Biopharmaceuticals Ltd.
Plasma Fractionation Institute (Omrix-PFI), MDA Services Center
Sheba Medical Center
Ramat Gan 5262000
POB 888
Kiryat Ono 5510801
Israel

Human Fibrinogen:
Omrix Biopharmaceuticals Ltd.
Jerusalem Plant (Omrix-JP)
5 Kiryat Hamada St.,
Ramot Meir Building
Har-Hotzvim P.O.B. 45075
Jerusalem 9777605
Israel

Name and address of the manufacturer(s) responsible for batch release
Omrix Biopharmaceuticals N.V.
Leonardo Da Vincilaan 15
1831 Diegem
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**.

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The Marketing Authorization Holder (MAH) shall perform the required pharmacovigilance

activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Carton (10.2 cm x 10.2 cm, 5.1 cm x 10.2 cm) and Foil Sachet (10.2 cm x 10.2 cm)

1. NAME OF THE MEDICINAL PRODUCT

EVARREST Sealant Matrix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

EVARREST contains per cm^2

Human Fibrinogen	8.1 mg
Human Thrombin	40 IU

3. LIST OF EXCIPIENTS

Excipients:
Composite Matrix (Polyglactin 910 and oxidised regenerated cellulose)
Arginine hydrochloride
Glycine
Sodium chloride
Sodium citrate
Calcium chloride
Human albumin
Mannitol
Sodium acetate

4. PHARMACEUTICAL FORM AND CONTENTS

Contains one sealant matrix (10.2 cm x 10.2 cm)

Contains two sealant matrices (5.1 cm x 10.2 cm)
2 units

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For epilesional use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Omrix Biopharmaceuticals N.V.
Leonardo Da Vincilaan 15
1831 Diegem
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/868/001
EU/1/13/868/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER-2DBARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Foil Sachet (5.1 cm x 10.2 cm)

1. NAME OF THE MEDICINAL PRODUCT

EVARREST Sealant Matrix

EVARREST contains per cm^2

Human Fibrinogen	8.1 mg
Human Thrombin	40 IU

Contains one sealant matrix (5.1 cm x 10.2 cm)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Omrix Biopharmaceuticals N.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For epilesional use.
Read the package leaflet before use.

Do not store above 25°C. Do not freeze.

EU/1/13/868/002

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

EVARREST Sealant Matrix

Human Fibrinogen / Human Thrombin

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before this medicine is used to treat you, because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What EVARREST is and what it is used for

EVARREST is a combination product made from an absorbable material (Matrix) coated with human fibrinogen and human thrombin.

Fibrinogen is a protein extracted from the blood that forms a fibrin clot when acted upon by the enzyme thrombin. When the dry powder coating of EVARREST is wetted, the thrombin acts on the fibrinogen to rapidly form a clot. The fibrin clot becomes embedded in the Matrix which enables EVARREST to stick firmly to the surrounding tissue.

EVARREST is applied during surgical operations in adult subjects, to stop bleeding and oozing during the operation. It is applied directly onto tissue where it sticks firmly and stops bleeding. It is left in place after the operation and is absorbed by the body.

2. What you need to know before you are treated with EVARREST:

Your surgeon must not treat you with EVARREST in the following circumstances:

EVARREST must not be applied inside blood vessels.

You must not be treated with EVARREST if you are allergic to human fibrinogen or human thrombin or to any of the other ingredients of this medicine (listed in section 6).

EVARREST must not be used to repair injuries to the wall of large arteries or veins where the product is exposed to constant blood flow and pressure.

EVARREST must not be used in closed spaces (for example, in, around, or next to openings or passages in the bone or other restricted areas around bone) where it could swell and compress nerves or blood vessels.

EVARREST must not be used in the presence of active infection or in contaminated areas of the body because infection may occur.

Warnings and precautions

Talk to your surgeon before you are treated with EVARREST.

Applications for which adequate data are not available
The use of EVARREST has not been studied in the following procedures, and there is therefore no information to show that it would be effective:

- surgery to the brain or spinal cord
- controlling bleeding in the stomach or intestines by applying the product through an endoscope (tube)
- sealing surgical repairs to the intestines.

Foreign body reactions
As with any product which is implanted, the body may develop a reaction to the foreign material. This could result in problems with healing. EVARREST should only be used in a single layer with an overlap of approximately 1 to 2 cm onto non-bleeding tissue to help it stick to the bleeding area. The size of EVARREST should be limited to what is necessary to stop bleeding.

Hypersensitivity reactions
Allergic-type hypersensitivity reactions are possible. Signs of such reactions include hives, rash, tightness of the chest, wheezing, drop in blood pressure, and anaphylaxis (a severe reaction with a rapid onset). If these symptoms occur during surgery, the use of the product should be stopped immediately.

Transmission of infectious agents
When medicines are made from human blood or plasma, certain measures are put into place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded.
- the testing of each donation and pools of plasma for signs of viruses/infections.
- the inclusion of steps in the processing of the blood and plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are given, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses, or other types of infections.

The measures taken in the manufacture of fibrinogen and thrombin are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped virus, hepatitis A. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g., sickle cell disease or haemolytic anaemia).

It is strongly recommended that every time you are treated with EVARREST, the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Children and adolescents

EVARREST is not recommended for use in children and adolescents under 18 years of age.

Other medicines and EVARREST

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.

Pregnancy, breast-feeding and fertility

There is not enough information available to know whether any particular risks are associated with the use of EVARREST during pregnancy or whilst breast-feeding, or whether it could affect fertility. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

EVARREST contains sodium

This medicine contains up to 3.0 mmol (68.8 mg) sodium in each EVARREST sealant matrix. This should be taken into consideration by patients on a controlled sodium diet.

3. How EVARREST is used

The surgeon will apply EVARREST during your operation. It is applied by pressing firmly onto bleeding tissue for approximately 3 minutes. EVARREST is activated upon contact with blood or other fluid and will stick firmly to the tissue. It is left in place and is absorbed by the body in approximately 8 weeks.

EVARREST can be cut to the size and shape required to fit the size of the bleeding area. The amount of EVARREST that will be applied depends on the surface area and location of the bleeding site to be treated during the operation. EVARREST should only be used in a single layer. Up to the equivalent of two 10.2 cm x 10.2 cm units or four 5.1 cm x 10.2 cm units should be used if needed to cover the entire bleeding area, with an overlap of approximately 1 to 2 cm. If bleeding still occurs, the EVARREST sealant matrix can be removed, and a new one can be applied.

The total amount of EVARREST left in the body after the operation should not exceed the size of two 10.2 cm x 10.2 cm sealant matrices or four 5.1 cm x 10.2 cm sealant matrices.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following adverse events which occurred during clinical studies were considered to be related to the use of EVARREST:

Most Serious Side Effects
Bleeding (haemorrhage)

- From the connection of two vessels (anastomotic haemorrhage); the frequency was uncommon (may affect up to 1 in 100 people).
- From the stomach (intra-abdominal haemorrhage); the frequency was uncommon (may affect up to 1 in 100 people).
- During surgery (operative haemorrhage); the frequency was uncommon (may affect up to 1 in 100 people).
- After surgery (post-procedural haemorrhage); the frequency was uncommon (may affect up to 1 in 100 people).

Blood clot (thromboembolism)

- In the veins, particularly of the legs (deep vein thrombosis)
- In the arteries supplying the lungs (pulmonary embolism)
  The frequency of both of these effects was uncommon (may affect up to 1 in 100 people).

Unintentional fluid intake into the airway (aspiration), build up of excess fluid in the cavity surrounding the lungs; the frequency was uncommon (may affect up to 1 in 100 people).

Accumulation of fluid in the stomach, swelling of the stomach; the frequency was uncommon (may affect up to 1 in 100 people).

Accumulation of fluid in the pancreas: the frequency was uncommon (may affect up to 1 in 100 people).

Increase in the levels of fibrinogen in the blood: the frequency was uncommon (may affect up to 1 in 100 people).

If you experience any symptoms such as vomiting with blood, blood in your stool, blood in your draining tube from your abdomen, swelling or skin discolouration in your extremities, chest pain and shortness of breath, and/or any other symptoms related to your surgery, please contact your doctor or surgeon immediately.

EVARREST contains the components of fibrin sealant. Fibrin sealants may, in rare cases (up to 1 in 1,000 people), cause an allergic reaction. If you experience an allergic reaction you might have one or more of the following symptoms: swelling under the skin (angioedema), skin rash, hives or wheals (nettle-rash), tightness of the chest, chills, flushing, headache, low blood pressure, lethargy, nausea, restlessness, increased heart rate, tingling, vomiting, or wheezing. If you experience any of these symptoms after surgery you should consult your doctor or surgeon.

There is a also a theoretical possibility that you could develop antibodies to the proteins in EVARREST, which could potentially interfere with blood clotting. The frequency of this type of event is not known (cannot be estimated from available data).

Reporting of side effects
If you get any side effects, talk to your doctor or surgeon. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How EVARREST is stored

EVARREST must be kept out of the sight and reach of children.

EVARREST must not be used after the expiry date which is stated on the foil sachet as well as the carton after EXP. The expiry date refers to the last day of that month.

EVARREST must not be stored above 25°C and must not be frozen.

EVARREST must be kept dry at all times prior to application to avoid pre-activation.

The foil sachet protects EVARREST from moisture and from microbiological contamination.

6. Contents of the pack and other information

What EVARREST contains

- The active substances are as follows:
  - Human fibrinogen (8.1 mg/cm^2)
  - Human thrombin (40 IU/ cm^2)

- The other ingredients are:
  - Composite Matrix (Polyglactin 910 and oxidised regenerated cellulose)
  - Arginine hydrochloride
  - Glycine
  - Sodium chloride
  - Sodium citrate
  - Calcium chloride
  - Human albumin
  - Mannitol
  - Sodium acetate

What EVARREST looks like and contents of the pack

EVARREST is presented as a sealant matrix which is 10.2 cm x 10.2 cm in size. Pack size of 1 and as sealant matrices which are 5.1 cm x 10.2 cm in size, Pack size of 2.

Marketing Authorisation Holder and Manufacturer

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Belgium
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Telefax: + 32 2 746 30 01

For any information about this medicine, please contact the Manufacturer:

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Plasma Fractionation Institute (Omrix-PFI), MDA Services Center
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This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Instructions for Use

Read this before you open the package

Handling of EVARREST

EVARREST comes ready to use in sterile packages and must be handled using sterile technique in aseptic conditions. Discard damaged packages as re-sterilisation is not possible.

To open the product, remove the foil sachet from the carton, carefully peel open the foil sachet avoiding contact with the inside of the foil or the white sterile tray containing EVARREST.

Remove the white sterile tray from the pouch and place onto the sterile field.

Hold the tray securely in the palm of the hand, ensuring that the side with the holes is facing upwards, and use the tabs on the side of the tray to remove the top of the tray with the other hand.

The lower portion of the tray contains EVARREST with the active side facing downwards. The active side is powdery in appearance. The non-active side has an embossed wave pattern.

Keep EVARREST dry after opening. The EVARREST sealant matrix can remain in the sterile field to be available for use throughout the procedure. EVARREST does not stick to gloves, forceps, or surgical instruments.

Storage of EVARREST

Do not use after the expiry date stated on the carton and label.

Keep out of sight and reach of children.

Do not store above 25°C. Do not freeze.

Application of EVARREST

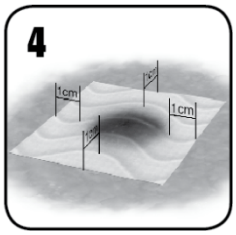
For epilesional use only. EVARREST is to be applied with approximately 3 minutes of firm manual compression.

1. Using sterile scissors, carefully cut EVARREST to the size and shape as necessary to fit and maintain contact with the bleeding area with an overlap of approximately 1 to 2 cm. Keep the powdery white-to-yellow colour active side of EVARREST facing down while in the tray.

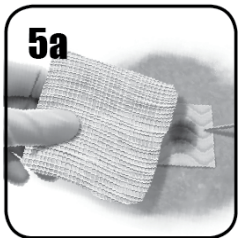
2. Remove excess blood or fluid from the site of application if required to improve visibility. The bleeding source should be clearly identified and it must be ensured that EVARREST is applied directly onto the bleeding source by covering it completely. EVARREST can be used in an actively bleeding field.

3. Apply the active side of EVARREST to the bleeding area, allowing full contact with the tissue. The product is activated upon contact with fluid, and adheres and conforms to tissue.

4. Apply an appropriately sized piece of EVARREST to adequately cover the entire bleeding area, with an overlap of approximately 1 to 2 cm onto non-bleeding tissue, to assist with adherence to the wound site.

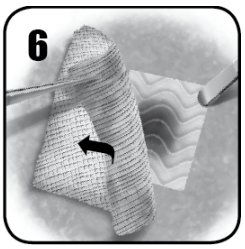


5a) Hold dry or moist surgical gauze or laparotomy pads over EVARREST to achieve full contact with the bleeding surface.



5b) To ensure haemostasis, immediately apply manual compression over the entire surface of the EVARREST (including the area of overlap) sufficient to stem all bleeding. Maintain compression for approximately 3 minutes, to control the bleeding.

6. Gently remove surgical gauze or laparotomy pads from the application site, without disrupting or dislodging EVARREST or the clot. Inspect EVARREST to verify that haemostasis has been achieved and to ensure that there is no crimping over the bleeding area. If not satisfied with the placement, remove EVARREST and use a new EVARREST sealant matrix. EVARREST will remain in place and adhere to the tissue, and is absorbable.



7. The application site should be monitored intraoperatively to verify that haemostasis is maintained.

Re-Treatment

- Re-treatment may be required if there are folds, creases, or crimps in the EVARREST sealant matrix. If not satisfied with the placement of EVARREST, remove the used EVARREST sealant matrix and repeat the application procedure above with a new EVARREST sealant matrix.

- If bleeding is due to insufficient coverage of the bleeding area, additional EVARREST sealant matrices may be applied. Apply in a single layer; ensure that the edges overalap (by approximately 1 to 2 cm) with the existing EVARREST sealant matrix.

- If bleeding is due to incomplete adherence to the tissue (where bleeding persists from under the dressing), remove EVARREST sealant matrix and use a new one.

- If bleeding still occurs during or after the specified duration of compression, remove the used EVARREST sealant matrix and inspect the bleeding site. If no other primary haemostatic measures (i.e., standard surgical techniques) appear to be required, repeat the application procedure above with a new EVARREST sealant matrix.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.