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

VeraSeal solutions for sealant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1:
Human fibrinogen 80 mg/ml

Component 2:
Human thrombin 500 IU/ml

Produced from the plasma of human donors.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solutions for sealant.

Frozen solutions. After thawing, the solutions are clear or slightly opalescent and colourless or pale yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment in adults where standard surgical techniques are insufficient:

- for improvement of haemostasis.
- as suture support: in vascular surgery.

4.2 Posology and method of administration

The use of VeraSeal is restricted to experienced surgeons who have been trained in the use of this medicinal product.

Posology

The volume of VeraSeal to be applied and the frequency of application should always be oriented towards the underlying clinical needs for 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.

Application of the product must be individualised by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.3 to 12 ml. For other procedures, larger volumes may be required.

The initial volume of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

Paediatric population
The safety and efficacy of VeraSeal in children aged 0 to 18 years has not yet been established. Currently available data are described in section 5.1, but no recommendation on a posology can be made.

Method of administration

For epilesional use.

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

Prior to applying VeraSeal, the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).

To avoid the risk of potentially life-threatening air or gas embolism, VeraSeal is recommended to be sprayed using pressurised CO_2.

For spray application, see sections 4.4 and 6.6 for specific recommendations on the required pressure and distance from tissue per surgical procedure.

4.3 Contraindications

VeraSeal must not be applied intravascularly.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

VeraSeal must not be used for the treatment of severe or brisk arterial bleeding.

Spray application of VeraSeal must not be used in endoscopic procedures. For laparoscopy, see section 4.4.

4.4 Special warnings and precautions for use

Precautions for use

For epilesional use only. Do not apply intravascularly.

Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly (see section 4.8).

Life-threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface.

The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and, therefore, cannot be excluded with VeraSeal. To minimize this risk, the spray device should be operated according to the instructions provided in section 6.6.

VeraSeal spray application should only be used if it is possible to accurately judge the spray distance, especially during laparoscopy. Spray distance from tissue and pressure should be within the ranges

recommended by the marketing authorisation holder of VeraSeal (see table in section 6.6 for pressure and distance).

When spraying VeraSeal, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

When using accessory tips, the instructions for use of the tips should be followed.

Before administration of VeraSeal, care must be taken that the parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites.

VeraSeal should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Adequate data are not available to support the use of this product in tissue gluing, neurosurgery, application through a flexible endoscope for treatment of bleeding or in gastrointestinal anastomoses.

Hypersensitivity reactions

As with any protein 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 administration must be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented.

Transmissible agents

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 infective 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 and hepatitis C virus, and for the non-enveloped hepatitis A virus. 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 increased erythropoiesis (e.g. haemolytic anaemia).

Traceability

It is strongly recommended that every time that VeraSeal is administered to a patient, the name and batch number of the product are recorded 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 formal 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

Pregnancy and breast-feeding

The safety of fibrin sealant/haemostatic products for use in human pregnancy or 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 breast-feeding women only if clearly needed.

Fertility

Fertility studies have not been conducted.

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 sealant/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.

Inadvertent intravascular injection could lead to thromboembolic event and disseminated intravascular coagulation (DIC), and there is also a risk of anaphylactic reaction (see section 4.4).

Life-threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of the spray device at higher than recommended pressures and/or near the tissue surface.

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

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention:

- 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)
- very rare (<1/10,000)
- not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing of seriousness.

Frequency of Adverse Reactions (ADRs) in clinical studies with VeraSeal:

MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
Infections and infestations	Abdominal abscess, cellulitis, liver abscess, peritonitis, postoperative wound infection, wound infection incision site infection, post procedural infection.	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Plasma cell myeloma	Uncommon
Blood and lymphatic system disorders	Anaemia, haemorrhagic anaemia, leukocytosis, leukopenia	Uncommon
Immune system disorders	Hypersensitivity*	Unknown
Metabolism and nutrition disorders	Hyperglycaemia, hyperkalaemia, hypocalcaemia, hypoglycaemia, hypokalaemia, hypomagnesemia, hyponatraemia, hypoproteinaemia	Uncommon
Psychiatric disorders	Anxiety, insomnia	Uncommon
Nervous system disorders	Headache, somnolence	Uncommon
Eye disorders	Conjunctival irritation	Uncommon
Cardiac disorders	Atrial fibrillation, ventricular tachycardia	Uncommon
Vascular disorders	Deep vein thrombosis, hypertension, hypotension	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, dyspnoea, hypoxia, pleural effusion, pleurisy, pulmonary oedema, rhonchi, wheezing	Uncommon
Gastrointestinal disorders	Nausea	Common
	Constipation, flatulence, ileus, retroperitoneal haematoma, vomiting	Uncommon
Skin and subcutaneous tissue disorders	Pruritus	Common
	Ecchymosis, erythema	Uncommon
Musculoskeletal and connective tissue disorders	Back pain, pain in extremity	Uncommon
Renal and urinary disorders	Bladder spasm, dysuria, urinary retention	Uncommon
General disorders and administration site conditions	Chills, hyperthermia, oedema peripheral, pain, pyrexia, vessel puncture site haematoma	Uncommon
Investigations	Parvovirus B19 test positive, activated partial thromboplastin time prolonged, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increase, blood glucose increase, international normalised ratio increased, prothrombin time prolonged, transaminases increased, urine output decreased	Uncommon

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency
	Drug specific antibody present*	Unknown
Injury, poisoning and procedural complications	Procedural pain	Common
	Abdominal wound dehiscence, post procedural bile leak, contusion, incision site erythema, incision site pain, post procedural haemorrhage, procedural hypotension, vascular graft complication, vascular graft thrombosis, wound secretion	Uncommon
*All these reactions are class effect. None were reported in clinical trials; thus it is not possible to establish frequencies.		

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

In the event of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment and supportive measures instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics, local hemostatics, ATC code: B02BC

Mechanism of action

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both, the conversion of fibrinogen and the crosslinkage of fibrin.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

Clinical efficacy and safety

Randomized, single-blind clinical studies with VeraSeal were conducted in subjects undergoing vascular, parenchymous tissue and soft tissue surgery demonstrating haemostasis, and suture support in vascular surgery.

During the vascular surgery study 225 subjects were enrolled and underwent vascular surgical procedures utilizing polytetrafluoroethylene graft material on end-to-side arterial anastomosis or on upper extremity vascular access arterial anastomosis. The mean age of the study population and its standard deviation was 63.2 (9.5) years. The most frequent surgery types were femoral-popliteal bypass grafting, upper extremity vascular access for hemodialysis, and ilio-femoral bypass grafting.

VeraSeal was shown to be superior to the control group (manual compression) in achieving hemostasis by 4 minutes. The rate of hemostasis at the target bleeding site by 4 minutes was 76.1% in the VeraSeal treatment group and was 22.8% in the control group.

During parenchymous tissue surgery study 325 subjects were enrolled and underwent liver resections. The mean age of the study population and its standard deviation was 57.9 (14.5) years. VeraSeal was shown to be superior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes. The rate of hemostasis at the target bleeding site by 4 minutes was 92.8% in the VeraSeal treatment group and was 80.5% in the control group.

During soft tissue surgery study 327 subjects were enrolled and underwent pelvic and retroperitoneal surgical procedures, and abdominoplasties and mastopexies. The mean age of the study population and its standard deviation was 47.2 (18.4) years. The most frequent surgery types were simple or radical hysterectomies, abdominoplasties, and radical cystectomies. VeraSeal was shown to be non-inferior to the control group (oxidized regenerated cellulose) in achieving hemostasis by 4 minutes. The rate of hemostasis at the target bleeding site by 4 minutes was 82.8% in the VeraSeal treatment group and was 77.8% in the control group.

Paediatric population

Eleven paediatric subjects aged 16 years or younger were treated with VeraSeal in the described clinical studies.

The European Medicines Agency has deferred the obligation to submit the results of studies with VeraSeal in one or more subsets of the paediatric population for the treatment of haemorrhage resulting from a surgical procedure as per Paediatric Investigational Plan (PIP) decision, for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

VeraSeal is intended for epilesional use only. Intravascular administration is contraindicated. Consequently, intravascular pharmacokinetic studies were not performed in man.

Fibrin sealant/haemostatic products are metabolised in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and acute toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human fibrinogen syringe

Sodium citrate dihydrated
Sodium chloride
Arginine
Isoleucine
Glutamic acid, monosodium
Water for injections

Human thrombin syringe

Calcium chloride
Human albumin
Sodium chloride
Glycine
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

After thawing, it can be maintained not more than 48 hours at 2ºC - 8ºC or 24 hours at room temperature (20ºC - 25ºC) before use if it remains sealed in the original packaging.

In use shelf life: Once the outer pouch is opened, VeraSeal should be used immediately.

6.4 Special precautions for storage

Store and transport in a freezer (at - 18 ºC or colder). The cold storage chain (- 18 ºC or colder) must not be interrupted until use. Keep the pouch containing the sterile blister in the outer carton to protect from light.

Once thawed, do not refreeze. For storage conditions after thawing the medicinal product and after first opening, see section 6.3.

6.5 Nature and contents of container

VeraSeal is supplied as a single-use kit containing two pre-filled syringes (glass type I) with rubber stoppers, each with a sterile frozen solution, assembled on a syringe holder.

One application cannula is supplied with the product.

VeraSeal may be applied with a spray application device, which is supplied separately.

VeraSeal is available in the following pack sizes:
- VeraSeal 2 ml (containing 1 ml of human fibrinogen and 1 ml of human thrombin)
- VeraSeal 4 ml (containing 2 ml of human fibrinogen and 2 ml of human thrombin)
- VeraSeal 6 ml (containing 3 ml of human fibrinogen and 3 ml of human thrombin)
- VeraSeal 10 ml (containing 5 ml of human fibrinogen and 5 ml of human thrombin)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

- **Thawing**

  Room temperature thawing

  VeraSeal should be thawed at room temperature (20 ºC - 25 ºC) for approximately eighty (80) minutes for the 2 ml and the 4 ml presentations and one hundred twenty (120) minutes for the 6 ml and the 10 ml presentations. The steps required for thawing are:

  - Open the cardboard case and take out the inner contents.
  - Place this packaging on a surface at room temperature.

  After thawing, it is not necessary to warm the product for its use.

  Water bath

  In case thawing times need to be shortened, a thermostatic water-bath could be used, but always at a temperature not higher than 37 ºC. At 37 ºC the times needed are approximately twenty (20) minutes for the 2 ml and the 4 ml presentations and thirty (30) minutes for the 6 ml and the 10 ml presentations. The steps required for thawing are:

  - Open the cardboard case and take out the inner contents.
  - Place this packaging into water bath.
  - Ensure this packaging remains submerged throughout thawing.

  The temperature must not exceed 37 ºC.

- **Preparation**

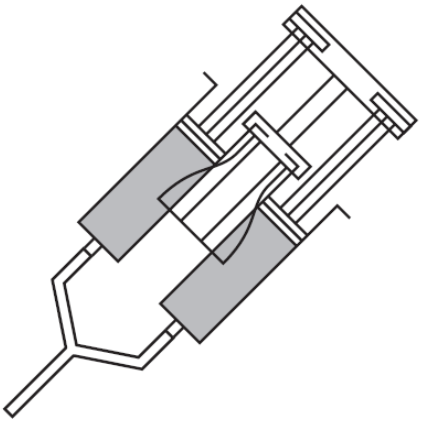
  After thawing the solutions must be clear to slightly opalescent and colourless to pale yellow. Solutions that are cloudy or have deposits should not be used.

  Transferring operations include:

  - Remove the packaging from surface at room temperature, from the refrigerator at 2 °C - 8 °C or from the water bath (and dry the outer pouch) after thawing.
  - Open the outer pouch and remove the sterile inner blister.
  - Open the inner blister and make the VeraSeal syringe holder available to a second person for transfer to the sterile field. The outside of the blister package should not come in contact with the sterile field.

  Connection operations include:

  - Hold the VeraSeal syringe holder slightly inclined upwards.
  - Unscrew and remove the tip cap of both fibrinogen and thrombin syringes.
  - To remove air bubbles from syringes, strike gently the side of the syringes one or two times while keeping the syringe holder in an upright position and eject air.
  - To attach the applicator tip, screw both syringes consecutively, making a quarter (90 degree) turn each time.



- **Application by dripping**

  VeraSeal must be applied with the syringe holder supplied.

  VeraSeal must be applied with the cannula provided with the product, or an equivalent CE-marked cannula (including open surgery and laparoscopic use devices) intended for that use. When using the provided cannula, follow the connection instructions described above. When using other applicator tips, the instructions for use of the tips should be followed.

  When dripped, the tip of the applicator should be kept as close as possible to the tissue surface, but without touching the tissue during application. Individual drops should be applied to the area to be treated.

  To prevent uncontrolled clotting, the drops should be allowed to separate from each other and from the tip of the applicator.

- **Application by spraying**

  VeraSeal must be applied with the syringe holder provided. VeraSeal should only be applied if it is possible to accurately judge the spray distance (see also section 4.4).

  VeraSeal must be applied with the spray device that is supplied separately, or an equivalent CE-marked spray device (including open surgery and laparoscopic use devices) intended for that use. Always refer to the specific instructions provided with the device packages.

  To avoid the risk of potentially life-threatening air or gas embolism VeraSeal is recommended to be sprayed using pressurised CO_2 (see table below).

  Connect the short gas tube on the application device to the luer-lock end of the filter tubing. Then connect the luer-lock of the gas tube to a pressure regulator capable of delivering 15 - 25 psi (1.0 - 1.7 bar) of gas pressure. The pressure regulator should be used in accordance with the manufacturer’s instructions.

  When applying VeraSeal using a spray device, it has to be ensured that the pressure and the distance from the tissue are within the ranges recommended by the marketing authorisation holder of VeraSeal, as given in the following table:

Surgery	Spray set to be used	Pressure regulator to be used	Recommended distance from target tissue	Recommended spray pressure
Open surgery	Spray device that is supplied separately, or equivalent	Compatible	10 cm (3.9 inches)	15 - 25 psi (1.0 - 1.7 bar)

The product should then be sprayed onto the surface of the tissue in short bursts (0.1 - 0.2 ml) to form a thin, even layer.

When spraying VeraSeal, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

- **Disposal**

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

7. MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
E-08150 Barcelona - Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1239/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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 SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Instituto Grifols, S.A.
Poligono Levante
c/Can Guasc 2
Barcelona
08150 Parets del Valles
SPAIN

Name and address of the manufacturer(s) responsible for batch release

Instituto Grifols, S.A.
Poligono Levante
c/Can Guasc 2
Barcelona
08150 Parets del Valles
SPAIN

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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 agreeed 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.

- **Additional risk minimisation measures**

Prior to launch of Veraseal in each Member State, the Marketing Authorisation Holder (MAH) must agree on the content and format of the educational material for use of Veraseal, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material is aimed at ensuring that all users of Veraseal via spray application are properly informed about the risk of air or gas embolism occurring with inappropriate administration technique with use of the spray device.

The MAH shall ensure that in each Member State where Veraseal is marketed, all healthcare professionals who are expected to use Veraseal have access to/are provided with the following educational package:

- Educational material for healthcare professionals
- Warning card (sticky tag) on the pressure regulator.

The educational material shall contain the following key elements:

- Description of the risk of life-threatening gas embolism if the product is sprayed incorrectly;
- Reinforced recommendation regarding the use of CO2 pressuring and the correct pressure and distance from tissue;
- Requirement to dry the wound using standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices) prior to using the product;
- Requirement to closely monitor blood pressure, pulse rate, oxygen saturation and end tidal CO2 when spraying the product, for the occurrence of gas embolism;
- Reminder of which pressure regulator(s) should be used, in line with manufacturer recommendations and the SmPC instructions for use.

The MAH shall ensure that a warning card/sticky tag is applied on the pressure regulator in use in each surgery unit. The warning card shall include the following key elements:

- Information on the maximum allowed pressure, and minimal distance to adhere to;
- Reminder that pressurised CO2 is recommended for use as spray gas for the spray application of Veraseal to avoid the risk of potentially life-threatening air or gas embolism.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX [2 ml, 4 ml, 6 ml and 10 ml]

1. NAME OF THE MEDICINAL PRODUCT

VeraSeal solutions for sealant

human fibrinogen / human thrombin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Component 1: 1 ml of human fibrinogen (80 mg/ml)
Component 2: 1 ml of human thrombin (500 IU/ml)

Component 1: 2 ml of human fibrinogen (80 mg/ml)
Component 2: 2 ml of human thrombin (500 IU/ml)

Component 1: 3 ml of human fibrinogen (80 mg/ml)
Component 2: 3 ml of human thrombin (500 IU/ml)

Component 1: 5 ml of human fibrinogen (80 mg/ml)
Component 2: 5 ml of human thrombin (500 IU/ml)

3. LIST OF EXCIPIENTS

Excipients:
human fibrinogen – Sodium citrate dihydrated, sodium chloride, arginine, isoleucine, glutamic acid, monosodium, water for injections.
human thrombin – Calcium chloride, human albumin, sodium chloride, glycine, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solutions for sealant

2 ml
4 ml
6 ml
10 ml

Two pre-filled syringes assembled on a syringe holder.
1 application cannula.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Epilesional 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

Store in a freezer (-18 ºC or colder). The cold storage chain must not be interrupted until use.
Keep the pouch containing the sterile blister in the outer carton in order to protect from light.

Thaw completely before use. Do not refreeze once thawed.
After thawing, it can be maintained not more than 48 hours at 2 ºC - 8 ºC or 24 hours at room temperature (20 ºC - 25 ºC) before use if it remains sealed in the original packaging. Once the packaging is opened, the product should be used immediately.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
E-08150 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1239/001 2 ml
EU/1/17/1239/002 4 ml
EU/1/17/1239/003 6 ml
EU/1/17/1239/004 10 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL OF THE STERILE BLISTER [2 ml, 4 ml, 6 ml and 10 ml]

1. NAME OF THE MEDICINAL PRODUCT

VeraSeal solutions for sealant

human fibrinogen / human thrombin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Component 1: 1 ml of human fibrinogen (80 mg/ml)
Component 2: 1 ml of human thrombin (500 IU/ml)

Component 1: 2 ml of human fibrinogen (80 mg/ml)
Component 2: 2 ml of human thrombin (500 IU/ml)

Component 1: 3 ml of human fibrinogen (80 mg/ml)
Component 2: 3 ml of human thrombin (500 IU/ml)

Component 1: 5 ml of human fibrinogen (80 mg/ml)
Component 2: 5 ml of human thrombin (500 IU/ml)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Solutions for sealant
2 ml
4 ml
6 ml
10 ml

Two pre-filled syringes assembled on a syringe holder.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Epilesional use.

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a freezer (-18 ºC or colder). The cold storage chain must not be interrupted until use. Keep the pouch containing the sterile blister in the outer carton in order to protect from light.
Thaw completely before use. Do not refreeze once thawed.
After thawing, it can be maintained not more than 48 hours at 2 ºC - 8 ºC or 24 hours at room temperature (20 ºC - 25 ºC) before use if it remains sealed in the original packaging. Once the packaging is opened, the product should be used immediately.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL – HUMAN FIBRINOGEN (1 ml, 2 ml, 3 ml and 5 ml)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VeraSeal solutions for sealant
Component 1: Fibrinogen 80 mg/ml
Epilesional use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml
2 ml
3 ml
5 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL – HUMAN THROMBIN (1 ml, 2 ml, 3 ml and 5 ml)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VeraSeal solutions for sealant
Component 2: Thrombin 500 IU/ml
Epilesional use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml
2 ml
3 ml
5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

VeraSeal solutions for sealant
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 you start using this medicine 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 VeraSeal is and what it is used for

VeraSeal contains human fibrinogen and human thrombin, two proteins extracted from the blood that form a clot when they are mixed together.

VeraSeal is used as a sealant during surgical operations in adults. It is applied to the surface of bleeding tissue to reduce bleeding during and after the operation when standard surgical techniques are not sufficient.

2. What you need to know before you are treated with VeraSeal

Your surgeon must not treat you with VeraSeal:

- if you are allergic to human fibrinogen or human thrombin or any of the other ingredients of this medicine (listed in section 6).

VeraSeal must not be applied inside blood vessels.

VeraSeal must not be used to treat severe or rapid bleeding from an artery.

VeraSeal must not be used by spraying in surgery carried out internally using an endoscope (a long flexible instrument for probing inside the body). For keyhole surgery (laparoscopy), the doctor will only use VeraSeal by spraying if the distance of the spray can be accurately judged (see below).

Warnings and precautions

Allergic reactions are possible. Signs of such reactions include hives, rash, tightness of the chest, wheezing, drop in blood pressure (e.g. light-headedness, fainting, blurred vision), and anaphylaxis (a

severe reaction with a rapid onset). If these symptoms occur during surgery, the use of the medicine should be stopped immediately.

Life-threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant products. This event occurs when air or gas bubbles enter a vein or artery and block it. This event appears to be related to the use of the spray device at higher than recommended pressures and/or near the tissue surface.

The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with VeraSeal. To minimize this risk, your surgeon will operate the spray device according to the instructions provided at the end of this leaflet.

VeraSeal spray application should only be used if it is possible to accurately judge the spray distance. A defined pressure within the range recommended should be used. In addition, the spray device should not be used closer than the recommended distance. When spraying VeraSeal, specific vitals will be monitored because of the possibility of occurrence of gas embolism. .

Special safety warning

For medicines such as VeraSeal that are made from human blood or plasma, certain measures are taken to prevent infections being passed on to patients. These include carefully selecting blood and plasma donors to make sure those at risk of carrying infections are excluded, and testing each donation and pooled plasma for signs of virus/infections. Manufacturers also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, 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 are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. 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 (fetal 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 VeraSeal, the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Children and adolescents

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

Other medicines and VeraSeal

The product may be affected after contacting solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions).

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

Pregnancy and breast-feeding

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 being treated with this medicine. Your doctor will decide whether you should be treated with VeraSeal.

3. How VeraSeal is used

The use of VeraSeal is restricted to experienced surgeons who have been trained in the use of VeraSeal.

The surgeon will apply VeraSeal to the surface of blood vessels or to the tissue surface of internal organs using an application device during the course of the operation. This device allows equal amounts of the two components of VeraSeal to be administered at the same time, and ensures that they mix evenly, which is important for the sealant to work at its best.

The amount of VeraSeal that will be applied depends on a number of factors, including the type of surgery, the size of the area to be treated during your operation and the way VeraSeal is applied. The surgeon will decide how much is appropriate, and will apply just enough to form a thin, even layer. If it does not seem to be enough, a second layer can be applied.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

VeraSeal contains the component 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 skin (angioedema), skin rash, hives or wheals (nettle-rash), tightness of the chest, chills, flushing, headache, low blood pressure, lethargy, nausea, restlessness, heart rate increase, tingling, vomiting or wheezing. In isolated cases, these reactions may progress to a severe allergic reaction. Allergic reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be allergic to constituents of the product. If you experience any of these symptoms after surgery, you should immediately consult your doctor or surgeon.

There is also a theoretical possibility that your immune system will produce proteins to attack VeraSeal and, that these may interfere with your blood clotting. The frequency of this type of event is not known.

If this product is accidentally placed inside a blood vessel, it can lead to blood clots, including disseminated intravascular coagulation (DIC) (when blood clots form throughout the blood vessels in the body). There is also a risk of a severe allergic reaction.

Side effects which were reported during clinical trials with VeraSeal included:

<u>Most serious side effects</u>

Uncommon (may affect up to 1 in 100 people):

- Abdominal abscess (swollen area in abdomen caused by infection)
- Abdominal wound dehiscence (wound breakdown due to incomplete healing)
- Leak of bile (a liquid produced by the liver) after the procedure
- Cellulitis (infection of the skin)
- Deep vein thrombosis (blood clots in the blood vessels)
- Liver abscess (swollen area in the liver caused by infection)
- Peritonitis (inflammation of the wall of the abdomen)
- Positive parvovirus B19 test (laboratory result showing infection with the virus)
- Postoperative wound infection
- Pulmonary embolism (blood clots in blood vessels in the lungs)
- Wound infection

Other side effects

Common (may affect up to 1 in 10 people):

- Nausea
- Pain caused by the surgery
- Pruritus (itching)

Uncommon (may affect up to 1 in 100 people):

- Anaemia (insufficiency of red blood cells)
- Anxiety
- Atrial fibrillation (irregular heartbeat)
- Back pain
- Bladder spasm
- Chills
- Conjunctival irritation (eye irritation)
- Constipation
- Contusion (bruise)
- Decreased urine output (reduced urine production)
- Dyspnoea (difficulty in breathing)
- Dysuria (pain or difficulty in urination)
- Ecchymosis (bruising)
- Erythema (reddening of the skin)
- Flatulence
- Headache
- High body temperature
- High or low blood pressure
- High or low levels of white cells in blood
- High potassium levels in blood
- Ileus (obstruction of the intestine)
- Impaired coagulation of blood
- Incision site erythema (reddening of the skin at the incision site)
- Incision site infection
- Increased blood bilirubin
- Increased levels of liver enzymes
- Increased or decreased glucose levels in blood
- Insomnia
- Low blood pressure due to the procedure
- Low calcium levels in blood
- Low magnesium levels in blood
- Low oxygen in blood
- Low potassium levels in blood
- Low protein levels in blood
- Low red blood cell levels caused by blood loss
- Low sodium levels in blood
- Oedema peripheral (accumulation of fluid)
- Pain, not specified
- Pain at the incision site
- Pain in extremity
- Plasma cell myeloma (cancer of blood cells)
- Pleural effusion (abnormal amount of fluid around the lung)
- Pleurisy (inflammation of lungs wall)
- Post procedural haemorrhage (bleeding after the procedure)
- Post procedural infection (infection after the procedure)
- Pulmonary oedema (excess of watery fluid in lungs)
- Retroperitoneal haematoma (accumulation of blood in the abdomen)

- Rhonchi (rattling lung sounds)
- Sleepiness
- Urinary retention
- Vascular graft complication (complication of vessel bypass)
- Vascular graft thrombosis (blood clots in blood vessel bypass)
- Ventricular tachycardia (rapid heartbeats)
- Vessel puncture site haematoma (bruising at site of vessel puncture)
- Vomiting
- Wheezing
- Wound secretion

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 VeraSeal is stored

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

VeraSeal must not be used after the expiry date which is stated on the label and carton after EXP.

It must be stored in a freezer at -18 ºC or colder. The cold storage chain must not be interrupted until use. Keep the pouch containing the sterile blister in the outer carton in order to protect from light. Thaw completely before use. Do not refreeze once thawed. After thawing, it can be maintained not more than 48 hours at 2 ºC - 8 ºC or 24 hours at room temperature (20 ºC - 25 ºC) before use.

Once the outer pouch is opened, VeraSeal should be used immediately.

It must not be used if the solutions are cloudy or have deposits.

6. Contents of the pack and other information

What VeraSeal contains

The active substances are:
- Component 1: Human fibrinogen
- Component 2: Human thrombin

The other ingredients are:
- Component 1: Sodium citrate dihydrated, sodium chloride, arginine, isoleucine, glutamic acid, monosodium, water for injections.
- Component 2: Calcium chloride, human albumin, sodium chloride, glycine, water for injections.

What VeraSeal looks like and contents of the pack

VeraSeal is presented as solutions for sealant. It is supplied as a single-use kit containing two pre-filled syringes assembled on a syringe holder. Frozen solutions. After thawing the solutions are clear or slightly opalescent and colourless or pale yellow.

One application cannula is supplied with the product.

VeraSeal may be applied with a spray application device, which is supplied separately.

VeraSeal is available in the following pack sizes:
- VeraSeal 2 ml (containing 1 ml of human fibrinogen and 1 ml of human thrombin)
- VeraSeal 4 ml (containing 2 ml of human fibrinogen and 2 ml of human thrombin)
- VeraSeal 6 ml (containing 3 ml of human fibrinogen and 3 ml of human thrombin)
- VeraSeal 10 ml (containing 5 ml of human fibrinogen and 5 ml of human thrombin)

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
E-08150 Barcelona - Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Other sources of information

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

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The following information is intended for healthcare professionals only:

Posology and method of administration

The use of VeraSeal is restricted to experienced surgeons who have been trained in the use of this medicinal product.

The volume of VeraSeal to be applied and the frequency of application should always be oriented towards the underlying clinical needs for 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.

Application of the product must be individualised by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.3 to 12 ml. For other procedures, larger volumes may be required.

The initial volume of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. VeraSeal should be applied as a thin layer. The application can be repeated, if necessary.

Incompatibilities

This medicinal product must not be mixed with other medicinal products.

Special precautions

For epilesional use only. Do not apply intravascularly.
Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

When using accessory tips, the instructions for use of the tips should be followed.

Before administration of VeraSeal, care must be taken that the parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites.

VeraSeal should be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Instructions for use

Read this leaflet before you open the package.

Handling of VeraSeal

VeraSeal 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.

- **Thawing**

  Room temperature thawing
  VeraSeal should be thawed at room temperature (20 ºC - 25 ºC) for approximately eighty (80) minutes for the 2 ml and the 4 ml presentations and one hundred twenty (120) minutes for the 6 ml and the 10 ml presentations. The steps required for thawing are:

  - Open the cardboard case and take out the inner contents.
  - Place this packaging on a surface at room temperature.

  After thawing, it is not necessary to warm the product for its use.

  Water bath
  In case thawing times need to be shortened, a thermostatic water-bath could be used, but always at a temperature not higher than 37 ºC. At 37 ºC the times needed are approximately twenty (20) minutes for the 2 ml and the 4 ml presentations and thirty (30) minutes for the 6 ml and the 10 ml presentations. The steps required for thawing are:

- Open the cardboard case and take out the inner contents.
- Place this packaging into water bath.
- Ensure this packaging remains submerged throughout thawing.

The temperature must not exceed 37 ºC.

- **Preparation**

After thawing the solutions must be clear to slightly opalescent and colourless to pale yellow. Solutions that are cloudy or have deposits should not be used.

Transferring operations include:

- Remove the packaging from the surface at room temperature, from the refrigerator at 2 °C - 8 °C or from the water bath (and dry the outer pouch) after thawing.
- Open the outer pouch and remove the sterile inner blister.
- Open the inner blister and make the VeraSeal syringe holder available to a second person for transfer to the sterile field. The outside of the blister package should not come in contact with the sterile field.

Connection operations include:

- Hold the VeraSeal syringe holder slightly inclined upwards.
- Unscrew and remove the tip cap of both fibrinogen and thrombin syringes.
- To remove air bubbles from syringes, strike gently the side of the syringes one or two times while keeping the syringe holder in an upright position and eject air.
- To attach the applicator tip, screw both syringes consecutively, making a quarter (90 degree) turn each time.

Please see pictogram at the end of this leaflet.

- **Application by dripping**

VeraSeal must be applied with the syringe holder supplied.

VeraSeal must be applied with the cannula provided with the product, or an equivalent CE-marked cannula (including open surgery and laparoscopic use devices) intended for that use. When using the provided cannula, follow the connection instructions described above. When using other applicator tips, the instructions for use of the tips should be followed.

When dripped, the tip of the applicator should be kept as close as possible to the tissue surface, but without touching the tissue during application. Individual drops should be applied to the area to be treated.

To prevent uncontrolled clotting, the drops should be allowed to separate from each other and from the tip of the applicator.

- **Application by spraying**

VeraSeal must be applied with the syringe holder provided. VeraSeal should only be applied if it is possible to accurately judge the spray distance (see also section 2).

VeraSeal must be applied with the spray device that is supplied separately, or an equivalent CE-marked spray device (including open surgery and laparoscopic use devices) intended for that use. Always refer to the specific instructions provided with the device packages.

To avoid the risk of potentially life-threatening air or gas embolism VeraSeal is recommended to be sprayed using pressurised CO_2 (see table below).

Connect the short gas tube on the application device to the luer-lock end of the filter tubing. Then connect the luer-lock of the gas tube to a pressure regulator capable of delivering 15 - 25 psi (1.0 - 1.7 bar) of gas pressure. The pressure regulator should be used in accordance with the manufacturer's instructions.

When applying VeraSeal using a spray device, it must be ensured that the pressure and the distance from the tissue are within the ranges recommended by the marketing authorisation holder of VeraSeal, as given in the following table:

Surgery	**Spray set to be used**	**Pressure regulator to be used**	**Recommended distance from target tissue**	**Recommended spray pressure**
Open surgery	Spray device that is supplied separately, or equivalent	Compatible	10 cm (3.9 inches)	15 - 25 psi (1.0 - 1.7 bar)

The product should then be sprayed onto the surface of the tissue in short bursts (0.1 - 0.2 ml) to form a thin, even layer.

When spraying VeraSeal, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

- **Disposal**

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