

1.4.3. PACKAGE INSERT (PI)

VeraSeal™
Solutions for sealant
Human fibrinogen / Human thrombin

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 *List of excipients*.

PHARMACEUTICAL FORM

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

CLINICAL PARTICULARS

Therapeutic indications

VeraSeal is indicated as supportive treatment in adults where standard surgical techniques are insufficient:
- for improvement of haemostasis.
- as suture support in vascular surgery.

Possology and method of administration

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

Possology

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 *Pharmacodynamic properties*, but no recommendation on a possology can be made.

Method of administration

For epileptical use.

For instructions on preparation of the medicinal product before administration, see section *Instructions for use, handling and disposal*. The product should only be administered according to the instructions and with the devices recommended for this product (see section *Instructions for use, handling and disposal*).
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).
For spray application, see sections *Special warnings and precautions for use* and *Instructions for use, handling and disposal* for specific recommendations on the required distance from tissue per surgical procedure.

Contraindications

VeraSeal must not be applied intravascularly.

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

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

Special warnings and precautions for use

Precautions for use

For epileptical use only. Do not apply intravascularly.

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

VeraSeal spray application should only be used if it is possible to accurately judge the spray distance, especially during laparoscopy. Spray distance from tissue should be within the range recommended by the marketing authorisation holder of VeraSeal (see section *Instructions for use, handling and disposal*).

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 (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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.

Fertility, pregnancy and lactation

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 studies have not been conducted.

Effects on ability to drive and use machines

Not relevant.

Undesirable effects

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 *Special warnings and precautions for use*).

For safety information with respect to transmissible agents, see section *Special warnings and precautions for use*.
Adverse reactions reported in clinical studies with VeraSeal are presented in the table below 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 seriousness.

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, hypomagnesaemia, 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
	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.		

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

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.

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 72.8% 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.

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

Pharmacokinetic properties

VeraSeal is intended for epileptical 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.

Preclinical safety data

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

PHARMACEUTICAL PARTICULARS

List of excipients

Human fibrinogen syringe: sodium citrate dihydrate, sodium chloride, arginine, L-isoleucine, L-glutamic acid monosodium, water for injection.
Human thrombin syringe: calcium chloride dihydrate, human albumin, sodium chloride, glycine, water for injection.

Incompatibilities

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

Shelf life

2 years.

After thawing, it can be maintained not more than 48 hours at 2 °C - 8 °C or 24 hours at room temperature (20 °C - 25 °C) before use if it remains sealed in the original packaging.
In use shelf life: Once the blister is opened, VeraSeal should be used immediately.

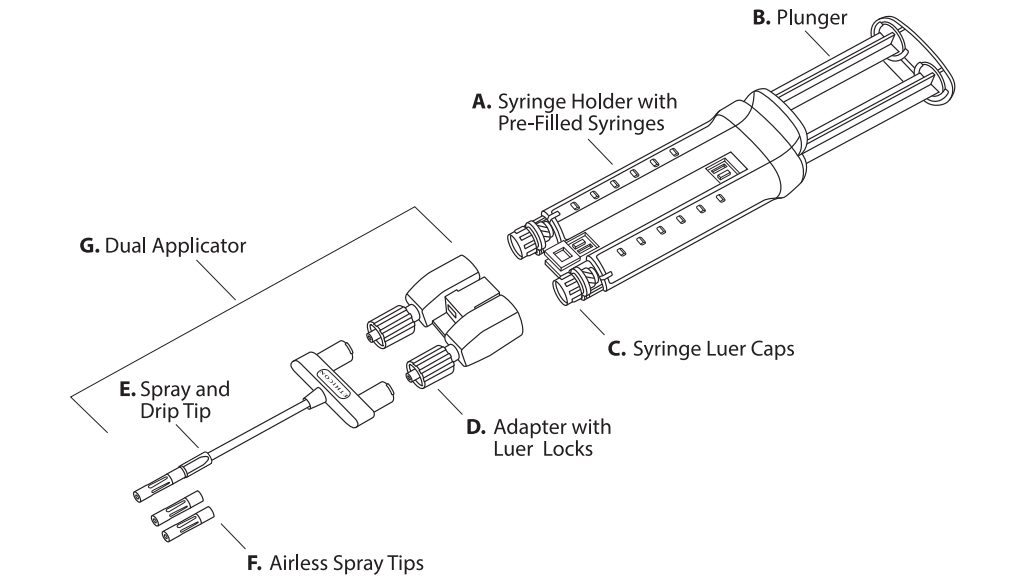
Special precautions for storage

Store and transport in a freezer (at -18 °C or colder). The cold storage chain (-18 °C or colder) must not be interrupted until use. Keep the sterilized blister in the outer carton to protect from light.
Thaw completely before use. Once thawed, do not refreeze. For storage conditions after thawing the medicinal product and after first opening, see section *Shelf life*.

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 in a syringe holder.

One Dual Applicator with two additional Airless Spray Tips is supplied with the product, for application by spraying or dripping. The Airless Spray Tips are radiopaque. See scheme below.



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.

Instructions for use, handling and disposal

Remove carton from freezer, open it and take out the two blisters.

Place the blister containing the Dual Applicator at room temperature until the fibrin sealant is ready to use.

Room temperature thawing (Preferred method)

Thaw blister with VeraSeal pre-filled syringes at room temperature using the following steps:

1. Place the blister containing the syringe holder with pre-filled syringes on a surface at room temperature (20 °C - 25 °C) for approximately 70 minutes for the 2 ml and the 4 ml package sizes for approximately 90 minutes for the 6 ml and the 10 ml package sizes

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

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.

Post-thawing Storage

The kit containing the VeraSeal syringe holder with pre-filled syringes and Dual Applicator can be stored before use for not more than 48 hours in the refrigerator at 2 - 8 °C or 24 hours at room temperature (20 - 25 °C) if it remains sealed in the original packaging. Once the blisters are opened, use VeraSeal immediately and discard any unused contents.

Once thawed, do not refreeze.

Transferring instructions

1. After thawing, remove the blister from surface at room temperature or from the refrigerator at 2 °C - 8 °C.
2. Open the blister and make the VeraSeal syringe holder with pre-filled syringes available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field. See Figure 1.



Figure 1

- **Sterile Water Bath (Quick thawing)**
Thaw VeraSeal pre-filled syringes inside the sterile field in a sterile thermostatic water bath at a temperature not higher than 37 °C using the following steps:
NOTE: Once the VeraSeal blisters are opened, use the product immediately. Use sterile technique to avoid the possibility of contamination due to improper handling, and follow the steps below accurately. Do not remove the syringe luer cap until thawing is complete and the Dual Applicator is ready to be attached.
1. Open the blister and make the VeraSeal syringe holder with pre-filled syringes available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field. See Figure 1.
2. Place the syringe holder with pre-filled syringes directly into the sterile water bath ensuring that it is completely immersed in the water. See Figure 2.
3. At 37 °C, the time needed is approximately 5 minutes for the 2 ml, 4 ml, 6 ml, and 10 ml package sizes, but must not be left at this temperature for longer than 10 minutes.
The temperature of the water bath must not exceed 37 °C.
4. Dry the syringe holder with pre-filled syringes after thawing, using a sterile surgical gauze.

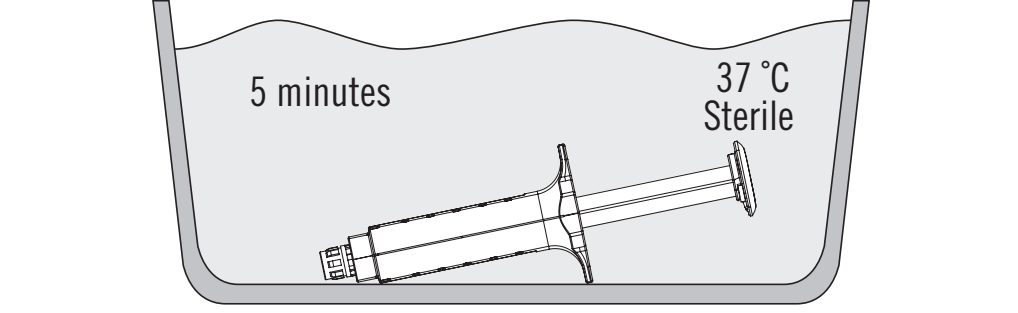


Figure 2

After thawing, the solutions must be clear to slightly opalescent and colorless to pale yellow. Do not use solutions that are cloudy or have deposits.
Use VeraSeal immediately and discard any unused contents.

Connection instructions

1. Open the blister and make the VeraSeal Dual Applicator and two additional Airless Spray Tips available to a second person for transfer to the sterile field. The outside of the blister should not come in contact with the sterile field.
2. Hold the VeraSeal syringe holder with syringe luer caps pointed upward. See Figure 3.
3. Unscrew and discard the syringe luer cap of both fibrinogen and thrombin syringes. See Figure 3.

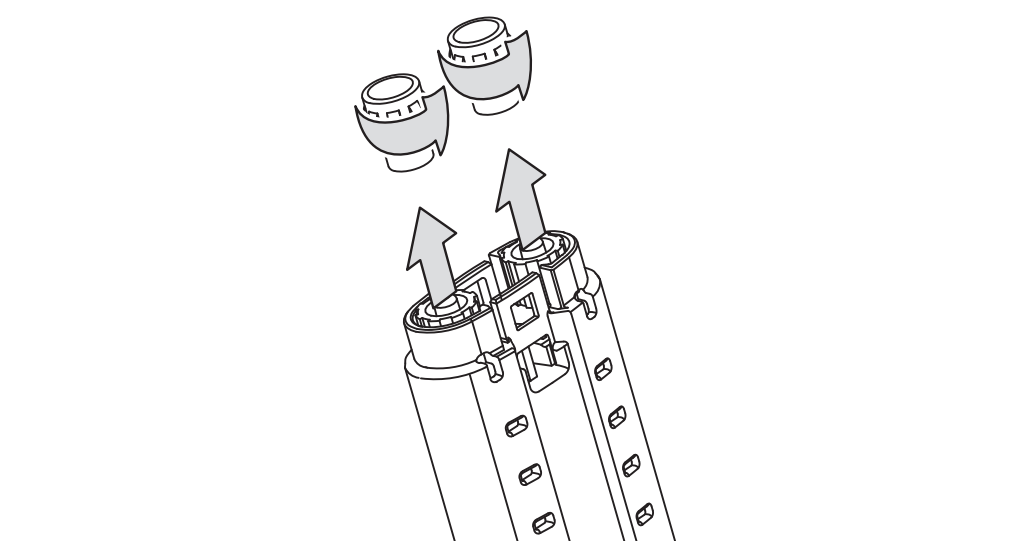


Figure 3

4. Hold the syringe holder with the luer's pointed upward. To remove air bubbles from syringes, strike gently the side of the syringe holder one or two times while keeping the syringe holder in an upright position and lightly depress the plunger to eject air. See Figure 4.

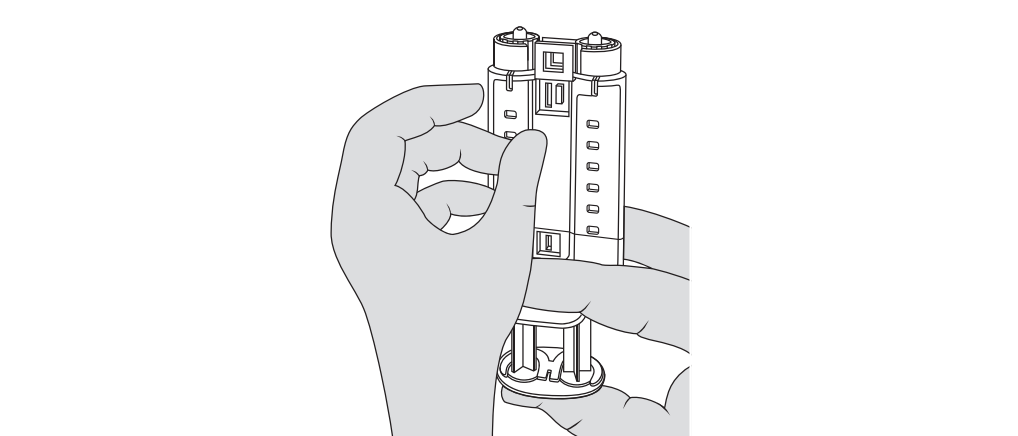


Figure 4

5. Attach the Dual Applicator. See Figure 5.
NOTE: Do not depress plunger during attachment or prior to intended use because the two biologic components will pre-mix in the Airless Spray Tip, forming a fibrin clot that prevents dispensing. See Figure 6.

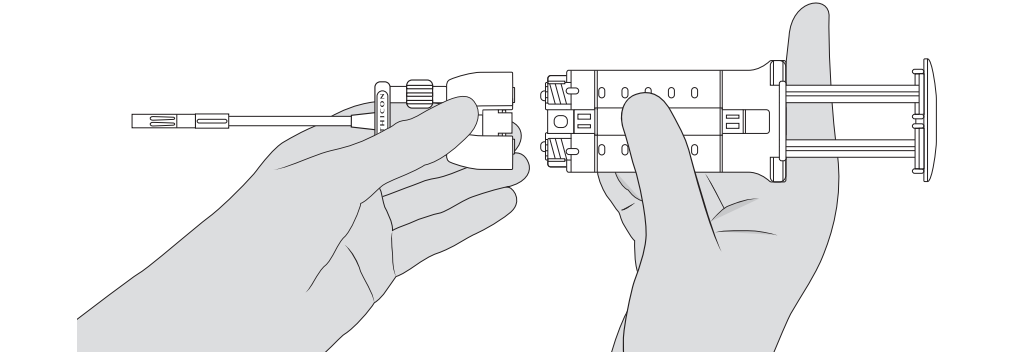


Figure 5

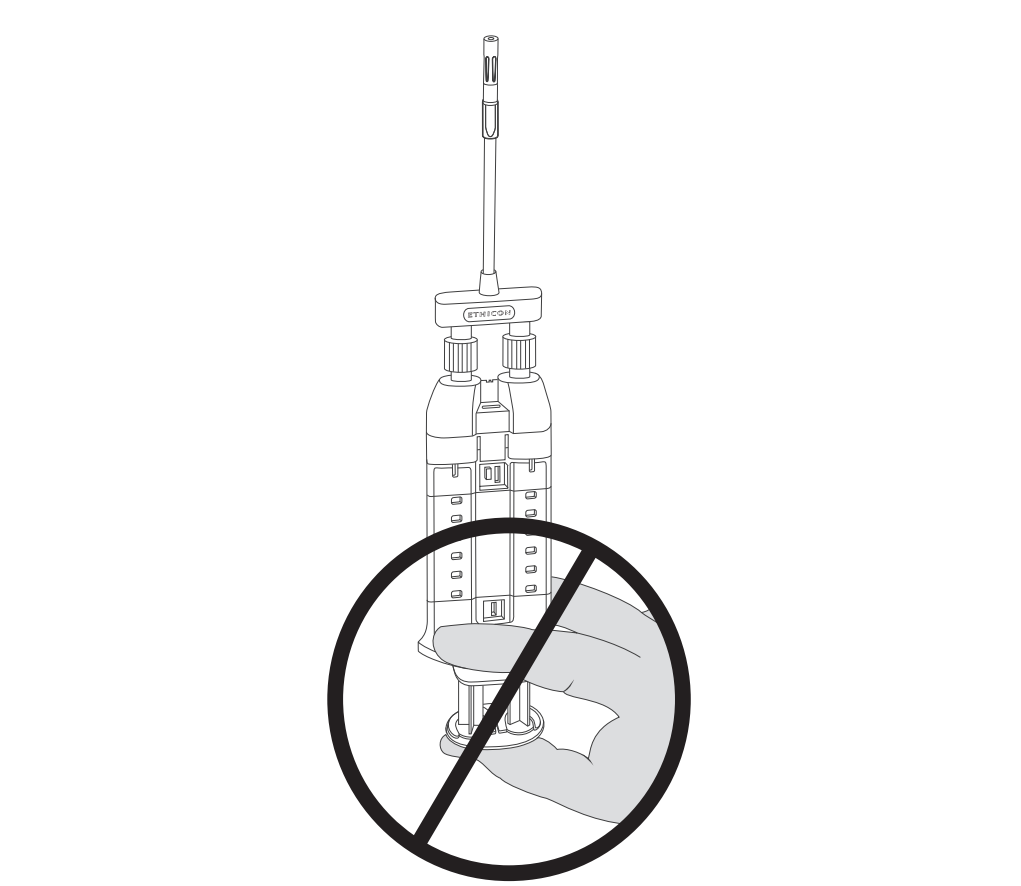


Figure 6

6. Tighten luer locks and ensure the Dual Applicator is firmly attached. The device is now ready to use.

Administration

Apply VeraSeal using the syringe holder and plunger supplied.
Apply VeraSeal using the Dual Applicator provided with the product. Other applicator tips authorised by Health Sciences Authority (HSA) (including open surgery and laparoscopic use devices) for specific use with VeraSeal may also be used. When using the provided Dual Applicator, follow the connection instructions described above. When using other applicator tips, follow the instructions for that are provided with the applicator tips.

Application by spraying

1. Grasp and bend the Dual Applicator to the desired position. Tip will retain its shape.
2. Position the Airless Spray Tip at least 2 cm away from the target tissue. Apply firm even pressure to the plunger to spray the fibrin sealant. Increase distance accordingly to achieve desired coverage of the target area.
3. If expression is stopped for any reason, change the Airless Spray Tip. To change the Airless Spray Tip, remove the device from the patient and unscrew the used Airless Spray Tip. See Figure 7. Place the used Airless Spray Tip away from the spare Airless Spray Tips. Wipe the end of the applicator using dry or moist sterile surgical gauze. Then, connect a new Airless Spray Tip provided in the package and ensure it is firmly connected before use.
NOTE: Red indicator will not be visible if Airless Spray Tip is properly connected. See Figure 8.
NOTE: Do not continue pushing the plunger in an attempt to clear the fibrin clot within the Airless Spray Tip, otherwise the applicator may become unusable.
NOTE: Do not trim the Dual Applicator to avoid exposing internal wire.

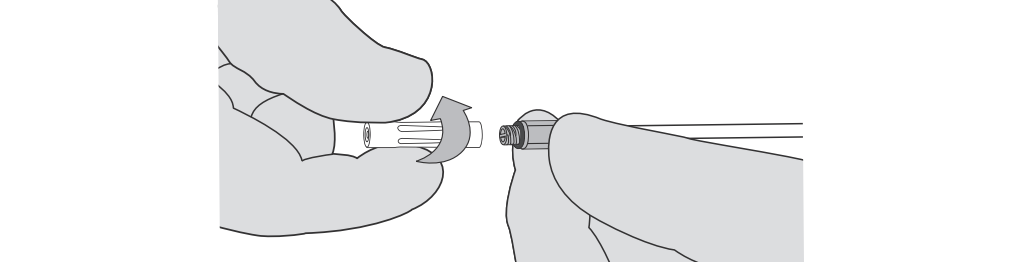


Figure 7

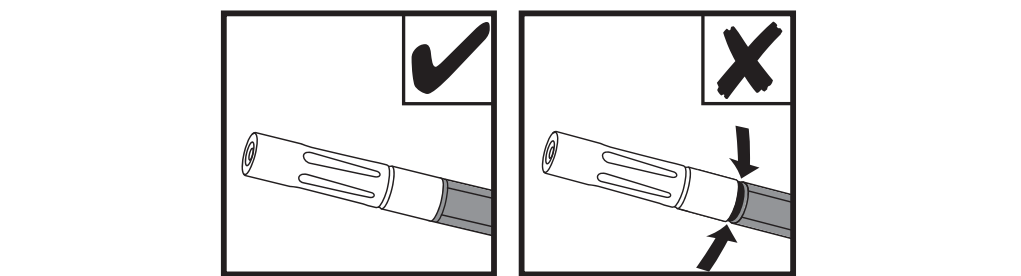


Figure 8

Application by dripping

1. Remove the Airless Spray Tip portion of the spray and drip tip by unscrewing the Airless Spray Tip. See Figure 7.
2. Grasp and bend the drip tip to the desired position. Tip will retain its shape.
3. During dripping, keep the end of the drip tip as close to the tissue surface as possible without touching the tissue during application.
4. Apply individual drops to the surface area to be treated. To prevent uncontrolled clotting, allow the drops to separate from each other and from the end of the drip tip.
NOTE: Do not reconnect a used drip tip after it has been removed from the adapter, otherwise a clot may form inside the drip tip and the applicator may become unusable.

Disposal

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

NAME AND ADDRESS OF MANUFACTURER

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

DATE OF REVISION OF THE TEXT