

Physician's Leaflet

VeraSeal™ solutions for sealant

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 epilepsional 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).

For spray application, see sections 4.4 and 6.6 for specific recommendations on the required 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.

4.4 Special warnings and precautions for use

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.

Precautions for use

For epilepsional use only. Do not apply intravascularly.

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

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 6.6).

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).

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

VeraSeal™ has no or negligible influence on the ability to drive and use machines.

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).

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 ($\geq 1/10$)
- common ($\geq 1/100$ to $< 1/10$)
- uncommon ($\geq 1/1,000$ to $< 1/100$)
- rare ($\geq 1/10,000$ 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.

Table 1. Frequency of adverse reactions (ARs) in clinical trials 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 |

| MedDRA system organ class (SOC) | Adverse reaction | Frequency |
|---|--|------------------|
| 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. | | |

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

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 cross linkage 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 trials 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.

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, dihydrate
Sodium chloride
Arginine
L-isoleucine
L-glutamic acid, monosodium
WFI (q.s.)

Human thrombin syringe

CaCl₂·2H₂O
Human albumin
Sodium chloride
Glycine
WFI (q.s.)

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After thawing, it can be maintained not more than 7 days at 2 °C - 8 °C or 24 hours not above 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.

6.4 Special precautions for storage

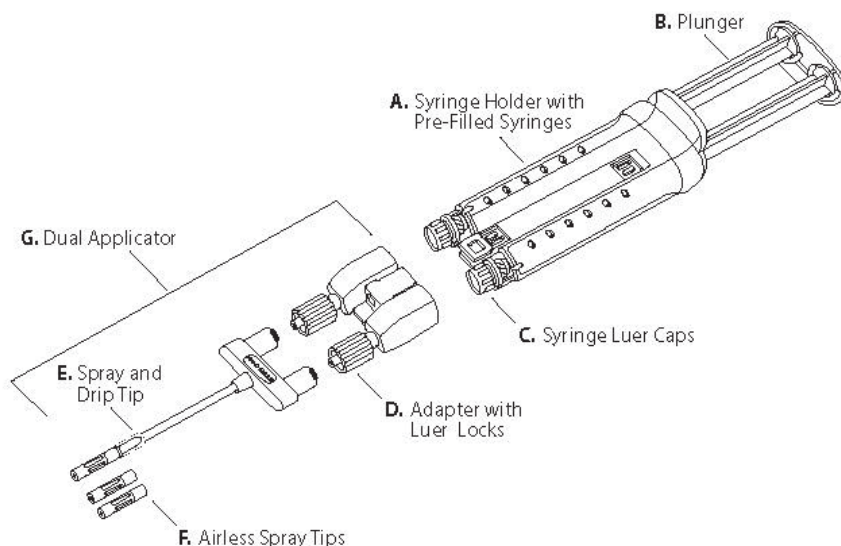
Store and transport in a freezer (at -18 °C or colder). The cold storage chain (-18 °C or colder) must not be interrupted until use. Keep the sterilized blister in the outer carton to protect from light.

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

6.6 Special precautions for disposal and other handling

An overview of thawing methods and storage after thawing is provided in Table 2.

Table 2. Thawing and storage after thawing

| Thawing method | Thawing time per package size | | Storage after thawing |
|----------------|-------------------------------|--------------------|-----------------------|
| | For 2 ml and 4 ml | For 6 ml and 10 ml | |
| | | | |

| | | | |
|---|---|---|---|
| Refrigerator (2 – 8 °C) | Minimum 7 hours | Minimum 10 hours | 7 days at 2 - 8 °C (refrigerator) in original package OR 24 hours not above 25 °C in original package |
| Thawing at 20 - 25 °C | Minimum 70 minutes | Minimum 90 minutes | |
| Sterile water bath (37 °C) inside sterile field | Minimum 5 minutes. Do not exceed 10 minutes. | Minimum 5 minutes. Do not exceed 10 minutes. | Use immediately during the surgery |

- **Preferred thawing methods**

Refrigerator thawing

1. Remove carton from freezer and place it in the refrigerator for thawing at 2 – 8 °C
a minimum of 7 hours for the 2 ml and the 4 ml package sizes
a minimum of 10 hours 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.

Do not use solutions that are cloudy or have deposits.

Thawing at 20 °C - 25 °C

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

Place the blister containing the Dual Applicator on a surface at 20 °C - 25 °C until the fibrin sealant is ready to use.

Thaw blister with VeraSeal™ pre-filled syringes at 20 °C - 25 °C using the following steps:

1. Place the blister containing the syringe holder with pre-filled syringes on a surface at 20 °C - 25 °C
a minimum of 70 minutes for the 2 ml and the 4 ml package sizes
a minimum of 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

After thawing, the kit containing the VeraSeal™ syringe holder with pre-filled syringes and Dual Applicator can be stored before use for not more than 7 days in the refrigerator at 2 - 8 °C or 24 hours not above 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 the surface at 20 °C - 25 °C or from the refrigerator at 2 °C - 8 °C.
2. Open the blister and confirm that the VeraSeal™ pre-filled syringes are completely thawed. 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)**

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

Place the blister containing the Dual Applicator on a surface at 20 °C - 25 °C until the fibrin sealant is ready to use.

Thaw VeraSeal™ pre-filled syringes inside the sterile field in a sterile thermostatic water bath at a temperature of 37±2 °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 39 °C.
4. Dry the syringe holder with pre-filled syringes after thawing, using a sterile surgical gauze.

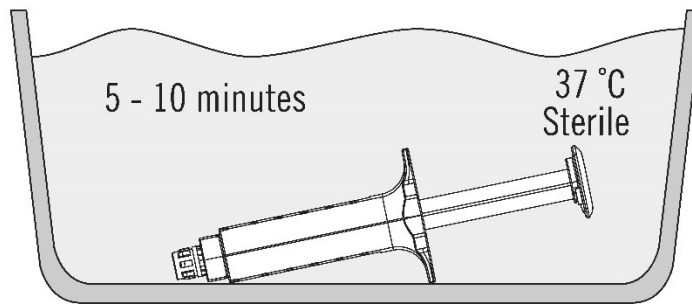


Figure 2

Confirm that the VeraSeal™ pre-filled syringes are completely thawed. 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.

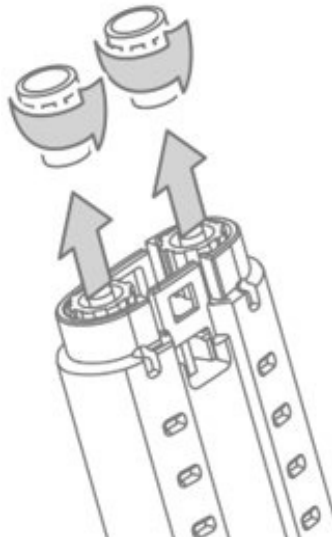


Figure 3

4. Hold the syringe holder with the luers 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.

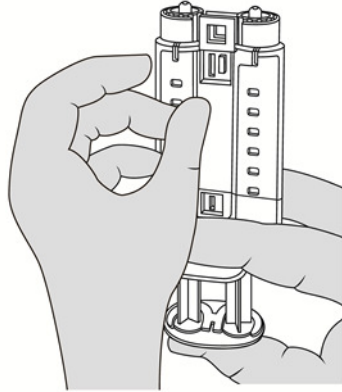


Figure 4

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.

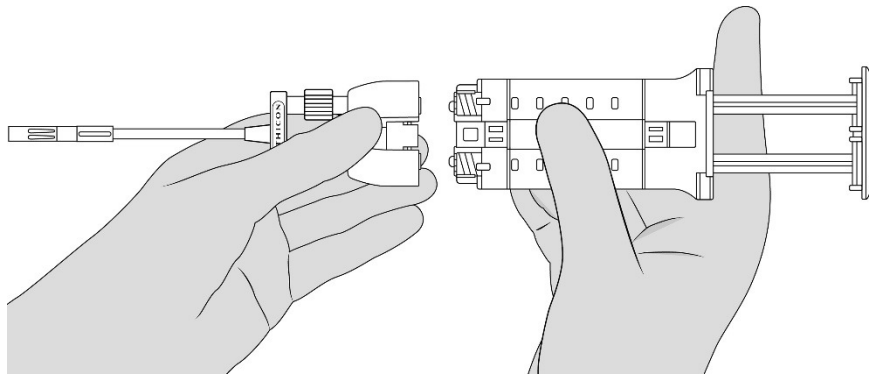


Figure 5

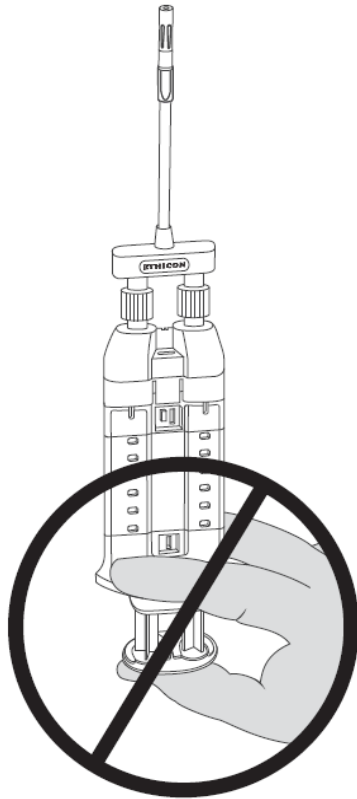


Figure 6

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 approved by Israel Ministry of Health (IMOH) (including open surgery and laparoscopic use devices) intended 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 use 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 prior to resuming application since a clot may form inside 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.

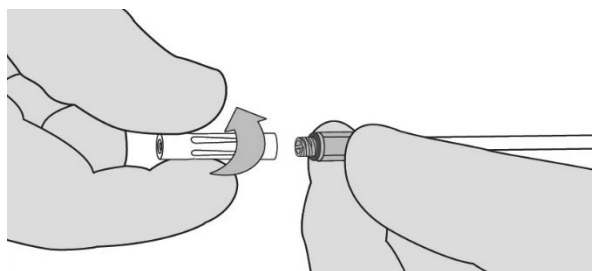


Figure 7

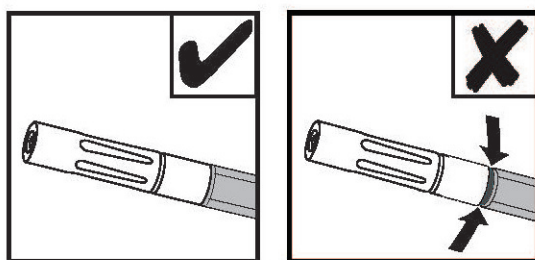


Figure 8

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.

7. Marketing Authorisation Holder

OMRIX Biopharmaceuticals
Kiryat Weizmann, Nes Ziona, Israel

8. Marketing Authorisation Number

172-78-36785-00

9. Manufacturer

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Barcelona, Spain.

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