FocalSeal-L Synthetic Absorbable Sealant
Caution: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

- **DESCRIPTION:**

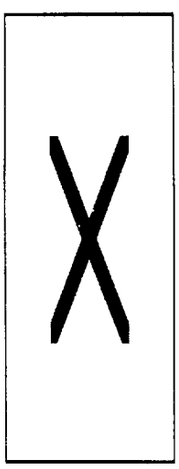
The FocalSeal-L Surgical Sealant system is comprised of synthetic absorbable sealant and primer solutions, two syringe/applicators, a light source, light wand and a PowerCap® light tester. The Sealant is formed via chemical and photochemical polymerization processes. The Sealant solution is provided in frozen form packaged in a red syringe and two primer vials. The two syringe applicators are used to deliver the primer and sealant solutions to the target tissue site. The FocalSeal reusable light source and light wand, ordered separately, photopolymerize the sealant solution to a thin film hydrogel. FocalSeal-L primer and sealant are aqueous solutions of poly (ethylene glycol) that have been modified with short segments of acrylate-capped poly (L-lactide) and poly (trimethylene carbonate). These solutions also contain buffers, initiators, and stabilizers (see section 8).

FocalSeal-L Surgical Sealant solutions (i.e., primer and sealant) are applied to the target tissue site as liquids. Upon exposure of the photo-initiator, Eosin-Y, to blue-green light, the primer and sealant solutions polymerize to form a crosslinked, clear, flexible, adherent hydrogel network. The sealant expands upon contact with body fluids and reaches its equilibrium swell volume within 24 hours. Over time the poly (L-lactide) and poly (trimethlyene carbonate) segments of FocalSeal-L Surgical Sealant degrade by hydrolysis, causing loss of mass and structural integrity. This results in the eventual dissolution and clearance of the Sealant via water-soluble molecules that are cleared through the kidneys or locally metabolized.

- **INDICATIONS:**

FocalSeal-L Sealant is intended for use as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.

Symbols



CE mark and identification number of notified body. Product conforms to the essential requirements of the Medical Device Directive. 93/42/EEC

See Instructions for Use

Batch Number

Method of Sterilization – Aseptic Fill Process

Method of Sterilization – Ethylene Oxide Gas

Temperature Indicator

22

Store ≤ -20°C
Use by year and month
Do not reuse/ resterilize
Fragile
Recycle
PowerCap light tester

Primer Vials
Red Sealant Syringe
Sealant Plunger
Primer/Sealant Applicators/Brushes
Primer Syringe/ Needle

- **CONTRAINDICATIONS:**

- FocalSeal-L Sealant is contraindicated for patients undergoing pneumonectomy or application over open or closed defects in main stem or lobar bronchi, due to an increased incidence of broncho-pleural fistulae observed in a clinical study in patients undergoing sleeve resection or bronchoplasty.

- FocalSeal-L Sealant is contraindicated for application on oxidized regenerated cellulose and absorbable gelatin sponges, as adherence will be compromised.

- **WARNINGS:**
  - The incidence of thoracic wound infection in the pivotal study was 9/125 (7.2%) in FocalSeal-L and 2/55 (3.6%) in control patients. A similar trend for bronchial infection was observed in the European study. Monitor the patient for infection and take appropriate therapeutic action as needed.
  - The incidence of empyema in the pivotal study was 4/125 (3.2%) in FocalSeal-L and 0/55 (0%) in control patients. Monitor the patient for empyema and take appropriate therapeutic action as needed.
  - The incidence of cancer progression in the pivotal study was 13/125 (10.4%) in FocalSeal-L and 4/55 (7.3%) in control patients at 6 months post surgery. FocalSeal-L's effect on the incidence and progression of cancer in humans is not known beyond six months. In a long-term resorption study of 20 months, the incidence of tumors in rats was similar between FocalSeal-L and historical controls.
  - FocalSeal-L use has not been studied in non-elective pulmonary resection cases.
  - FocalSeal-L use has not been studied in contaminated or dirty pulmonary resection cases.
  - FocalSeal-L use has not been studied in the presence of active infection.
  - FocalSeal-L use has not been studied with other sealants or hemostatic materials.
  - The safety and effectiveness of FocalSeal-L has not been evaluated in humans under 18 years of age, pregnant or nursing women.
  - Possible explosion hazard if light source is used in presence of flammable anesthetics
  - Illuminated light wand can cause permanent damage if viewed directly with unprotected eye.
  - Avoid placing the light wand on the patient or on surgical drapes while the 40-second light cycle is activated. Inadvertent activation of the light source while the tip of the light wand is in close proximity with skin or surgical drapes may cause burns and/or ignition of combustible material.
  - To avoid excessive tissue heating, keep light wand approximately 2 cm from tissue surface.
  - FocalSeal-L resorption time in humans has not been evaluated. 35% of FocalSeal-L was present in rats after six months and the device was essentially resorbed at 20 months.

- **PRECAUTIONS:**
  - FocalSeal-L should not be used in persons who are hypersensitive to hydroquinone or any of the other device components (see section 8).
  - The safety of FocalSeal-L applications has not been evaluated in patients receiving more than 12.5 ml of primer or 39.0 ml of sealant.
  - In clinical studies effective sealing only required application of a thin (approx. 1 mm thick) layer of sealant to the target tissue site.
  - Use of additives (e.g., antibiotics) to the sealant has not been studied.
  - The sealant, primer, applicators and Power Cap are for single use only. DO NOT RE-STERILIZE.
  - The light wand must be cleaned and sterilized prior to use. (Please refer to Section 12 of the Light Source / Light Wand manual).
  - FocalSeal-L Sealant is light sensitive. Do not remove FocalSeal-L Sealant from red sealant syringe. Apply only as described in these Instructions for Use.
  - Inspect sterile package and seal prior to use. Do not use if sterile package or seal is damaged or open. Discard unused material.
  - Prior to application of FocalSeal-L Sealant, ensure that the surgical procedure is complete, hemostasis has been achieved, and the lung is deflated to the point of no active air leaks.
  - If FocalSeal-L Sealant is not prepared and applied as described in these Instructions for Use, the adherence and/or mechanical properties of the material may be compromised.
  - During application of FocalSeal-L Sealant, the lung should not be ventilated.
  - Brush/apply FocalSeal-L Sealant within primer area only.
  - Avoid pooling of primer material on the lung surface.
  - Do not create bubbles in sealant material during application. Bubbles may appear as end of sealant supply is reached. If this occurs, use new sealant syringe.
  - Keep the light wand tip approximately 2 cm away from tissue surface so that sealant solution receives adequate light exposure, and application site can be polymerized in one light cycle.

- Do not use any mixed FocalSeal-L primer or sealant more than 8 hours old, as the adherence and/or mechanical properties of the material may be compromised.

- **ADVERSE REACTIONS:**

  Adverse events which occurred in the FocalSeal-L cohorts at an incidence of 1% or greater in the US study and 2.9% or greater in European study are listed in Tables 1 and 2, respectively. The adverse events are listed in descending order according to frequency. These tables list all adverse events reported in the study including those attributed and not attributed to treatment.

Summary of Adverse Events for U.S. Study

Table 1

	FocalSeal-L (n=125)		*Control (n=55)*	
Event	#	%	#	%
Arrhythmia	29	23.2	17	30.9
Fevers	15	12.0	8	14.5
Cancer Progression	13	10.4	4	7.3
Pneumothorax	10	8.0	4	7.3
Thoracic Wound Infection	9	7.2	2	3.6
Pneumonia	9	7.2	5	9.1
Death	7	5.6	4	7.3
Confusion	7	5.6	0	0
Upper Respiratory Infection	7	5.6	3	5.5
Anemia	6	4.8	5	9.1
Ileus / Intestinal Obstruction	5	4.0	2	3.6
Urinary Tract Infection	4	3.2	3	5.5
Empyema	4	3.2	0	0
Persistent Atelectasis	4	3.2	0	0
Pulmonary Emboli	3	2.4	0	0
Deep Vein Thrombosis	3	2.4	0	0
Pleural Effusion	3	2.4	0	0
Residual Space	3	2.4	0	0
Colitis / Gastroenteritis	3	2.4	0	0
Hemoptysis	2	1.6	0	0
CHF	2	1.6	0	0
COPD	2	1.6	0	0
Anxiety	2	1.6	2	3.6
Hypotension	2	1.6	0	0

In the clinical trial, 7/125 FocalSeal-L and 4/55 Control patients died during the time patients were on study. All deaths were judged by the investigator as not related to treatment. Regarding the severity of non-fatal adverse events, there were 66 severe events in 43 (34%) patients, 90 moderate events in 72 (58%) patients

and 27 mild events in 13 (10%) in the 125 FocalSeal-L patients. In the 55 control patients there were 30 severe events in 17 (31%) patients, 41 moderate events in 28 (51%) patients and 15 mild events in 4 (7%) patients.

Summary of Adverse Events for European Study
Table 2

Event	*FocalSeal-L (n=34)*	*Control (n=26)*
Bronchial Fistulae [associated events included infection (4) and pneumothorax (2)]	8 (23.5%)	0 (0%)
Out of Range Lab Values	6 (17.6%)	2 (5.9%)
Pneumonia	5 (14.7%)	1 (3.8%)
Bronchial Infection	5 (14.7%)	0 (0%)
Superficial Phlebitis	4 (11.8%)	0 (0%)
Death	2 (5.9%)	1 (3.8%)
Metastatic Disease	2 (5.9%)	1 (3.8%)
DVT	2 (5.9%)	0 (0%)
Pneumothorax	2 (5.9%)	1 (3.8%)
Respiratory Depression / Insufficiency	2 (5.9%)	1 (3.8%)
Fever and Leukocytosis	1 (2.9%)	2 (7.7%)
Urinary Tract Infection	1 (2.9%)	2 (7.7%)
Pulmonary Infiltrates	1 (2.9%)	1 (3.8%)
Cardiac Failure	1 (2.9%)	1 (3.8%)
Cardiac Tamponade	1 (2.9%)	1 (3.8%)
Hematoma	1 (2.9%)	1 (3.8%)
Pulmonary Embolism	1 (2.9%)	1 (3.8%)
Anemia	1 (2.9%)	1 (3.8%)
Sepsis	1 (2.9%)	1 (3.8%)

The following events occurred in one FocalSeal-L patient, but no control patients: pulmonary erosion, post-thoracotomy syndrome, effusion, atelectasis, bronchitis, pulmonary edema, arrythmia, lymphedema, intestinal obstruction, visual field defect, CVA, and vomiting.

In the clinical trial, 2/34 FocalSeal-L and 1/26 Control patients died during the time patients were on study. All deaths were judged by the investigator as not related to treatment

- **CLINICAL STUDIES:**

a) U.S. Study

An open label, prospective, randomized, multi-center study comparing standard tissue closure techniques (control) to standard tissue closure techniques plus the FocalSeal-L Sealant (treatment) in a total of 180

eligible patients scheduled to undergo elective pulmonary resections via an open thoracotomy procedure. Application of FocalSeal-L Sealant to the bronchial stump was contraindicated in this study. Patients were randomized to treatment or control in a 2:1 ratio and the first two treatment patients were prospectively identified as pilot patients and not included in the effectiveness analysis.

The primary efficacy endpoint was the proportion of patients determined to be air leak free at the end of the surgical procedure and who remained air leak free through hospital discharge. The secondary efficacy endpoints were mean time to air leak cessation and the proportion of patients air leak free at the end of the surgical procedure. Safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1, 3 and 6 months post-operatively.

Patient and Baseline Characteristics are presented in Table 3.

Patient and Baseline Characteristics[1]

Table 3

		FocalSeal-L (n=125)	Control (n=55)
Gender	Female	73 (58%)	24 (44%)
	Male	52 (42%)	31 (56%)
Age at Surgery (yrs)	Mean	62.1	62.1
	Range	31 – 75	21 - 75
	Std. Dev.	9.7	10.0
Primary Surgical Diagnosis	Pulmonary Cancer	90 (72%)	43 (78%)
	Pulmonary Metastasis	16 (13%)	7 (1%)
	Benign Neoplasis	8 (7%)	2 (4%)
	Other	11 (9%)	3 (5%)
Types of Surgery	Single Lobectomy	83 (66%)	28 (51%)
	Single Wedge	18 (14%)	7 (13%)
	Segmentectomy	8 (7%)	6 (11%)
	Bi-Lobectomy	8 (7%)	4 (7%)
	Other	8 (7%)	10 (18%)
Number of Patients with Air Leaks Prior to Randomization		95 (76%)	39 (71%)

[1]No statistically significant ($p<0.05$) differences were detected between groups.

The results of the US study are presented in Table 4.

Study Endpoint Results

Table 4

	FocalSeal-L (n=117)	Control (n=55)	p-Value
Patients Air Leak-Free through Hospital Discharge	39% (46/117)	11% (6/55)	0.001[1]
Patients Air Leak-Free at Skin Closure	92% (108/117)	29% (16/55)	0.001[1]
Time to Air Leak Cessation (Hrs)			0.006[2]
Mean (SE)	30.9 (4.8)	52.3 (11.6)	
Median	12.1	27.6	

[1] Mantel-Haenszel Test
[2] Generalized Wilcoxon Test comparing time to last air leak distribution

Analyses of additional data collected in the study are summarized in Table 5.

Additional Analyses

Table 5

	FocalSeal-L (n=125)	Control (n=55)	p-Value[1]
Days to Chest Tube Removal			
Mean (SE)	4.5 (0.2)	5.2 (0.5)	NS[1]
Median	4.0	4.0	
Days to Hospital Discharge			
Mean (SE)	7.4 (0.4)	10.1 (1.8)	NS
Median	6.0	6.0	
Days to Drainage < 125 cc/day			
Mean (SE)	3.4 (0.12)	3.7 (0.25)	NS
Median	3.0	3.0	
Patients with Recurrent Air Leak[2]	62/108 (57%)	10/16 (63%)	NS

[1] NS – Not statistically significant.
[2] In patients who were air leak free at skin closure, but subsequently developed a post-operative air leak, 93% and 90% of the air leaks in FocalSeal-L and Control patients, respectively, began within 24 hours after surgery.

b) European Study
This was an open label, prospective, randomized (1:1), multi-center study to compare standard tissue closure techniques (control; n=26) to standard tissue closure techniques plus FocalSeal-L Sealant (treatment; n=34) in a total of 60 eligible patients scheduled to undergo pulmonary resections.

The primary efficacy endpoint was the proportion of patients air leak free at the end of the surgical procedure. Safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1 and 2 months post-operatively.

The study population was predominantly male (70% of treatment group and 77% of control group) and the primary surgical diagnosis was bronchogenic carcinoma (77% of treatment group, 65% of control group). The primary surgical procedure was single lobectomy (83% of treatment group, 77% of control group).

The proportion of patients air leak free at the end of the surgical procedure was 100% in the treatment group and 27% in the control group (p=0.001).

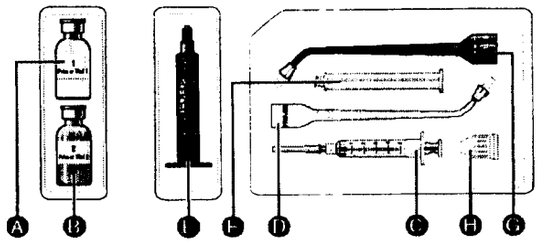
8) INSTRUCTION FOR USE:

Introduction
FocalSeal-L Sealant is intended for use as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection by placing a thin, adherent coating of a biocompatible and absorbable hydrogel onto tissue. Applied as a liquid, the FocalSeal-L Sealant flows and conforms to the target tissue site and is then chemically and photochemically polymerized to form a flexible, adherent hydrogel.

FocalSeal-L Sealant contains polymerizable macromers, composed of poly (ethylene glycol) modified with biodegradable and photo-reactive elements. The FocalSeal-L Sealant is formed by *in situ* polymerization of two aqueous pre-polymer solutions applied in 3-step process. In the first step, the primer solution is brushed onto the target site using the designated primer applicator. This step provides coverage of the tissue surface and facilitates flow of the low viscosity primer solution into the tissue interstices defined by the target surface topography. In the second step, the sealant solution is brushed onto the target tissue site using the sealant applicator. This step provides mixing of the sealant and primer solutions. In the third step, the sealant brush tip is removed and the sealant is applied directly over the target site in a continuous manner, allowing the sealant to flow in an uninterrupted layer approximately 1 mm thick, which is then illuminated with visible light

of a specified filtered wavelength by the light wand. This step provides photopolymerization, which completes the crosslinking of the primer and sealant molecules and results in formation of an adherent, flexible sealant.

HOW SUPPLIED:



Single-Use: All items are sterile.

One Frozen Material Set Containing:

One blister pack containing:

A. One Primer Vial 1 - 5 ml of a yellow solution material containing: fructose, ferrous gluconate and water for injection

B. One Primer Vial 2 - a pink solid lyophilized material containing: primer macromer, NaCl and Eosin Y

One blister pack containing:

E. One Red Sealant Syringe - 8 ml of FocalSeal-L Surgical Sealant, a pink viscous liquid, containing: sealant macromer, triethanolamine, KH_2PO_4, vinyl caprolactam, t-butyl hydroperoxide, Eosin Y, hydroquinone and water for injection

One Applicator Kit Containing:

C. One 5 ml syringe with a 16-gauge needle

D. One Primer applicator with brush

G. One Sealant applicator with brush

F. One plunger

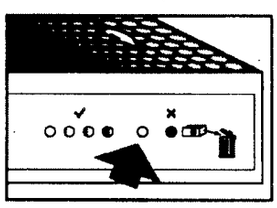
H. One PowerCap light tester

Reusable: Items are supplied non-sterile.

- One non-sterile, reusable light wand.
- One non-sterile, reusable light source and power cord.

Storage:

- Store the FROZEN FocalSeal-L Surgical Sealant and Primer in the material box at ≤ -20°C to maintain performance and keep its useful shelf life. Do not use after expiry date.
- A temperature indicator strip on the side of the frozen material box should be checked prior to use, to ensure that product has been stored at the appropriate temperature.



PRECAUTION:

- If the window on the indicator strip has turned completely blue, do not use. Discard the package and retrieve another frozen material set from the freezer.

- Applicator kit, light wand, and light source do not require any special storage conditions.

Sterility:

- Contents of material box and applicator kit are supplied sterile. FocalSeal-L Sealant and Primer are sterilized by aseptic fill processes. The FocalSeal applicator kit is sterilized by ethylene oxide gas.
- Do not use if sterile package is damaged or opened. Discard any unused material following the surgical procedure.
- The light wand is supplied non-sterile and must be cleaned and sterilized prior to use. Refer to the Light Source/Light Wand Instructions for Use.
- The light source is supplied non-sterile. Both light wand and light source are reusable.

Light Source / Light Wand Preparation

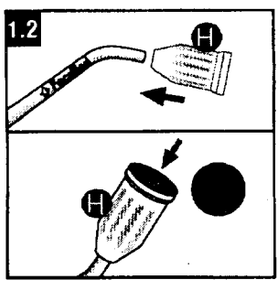
Note:

- *Do not remove PowerCap light tester during illumination cycle.*
- *To avoid inaccurate test results, wait 2 minutes between initial and repeat light source/light wand output tests.*
- *If the PowerCap light tester is not available, measure the light system output with an optical power meter (refer to the Light Source/Light Wand Instructions for Use).*

1.1 Turn the FocalSeal light source on five minutes prior to use. Refer to the FocalSeal Light Source/Light Wand Operating Instructions manual for complete description, warning and cautions.

Check that both the distal tip optical window and the optical connector of the light wand are clean prior to use of the PowerCap light tester.

1.2 Fully push the PowerCap light tester onto the distal end of the FocalSeal light wand. Turn light wand on for one complete (40 second) cycle. (Fluted sides of the tester illuminate blue during the light cycle.) Within one complete light cycle, a small colored circle will appear in the center of the black disk, at the end of the PowerCap light tester. Appearance of a colored circle indicates that the light source/light wand combination has sufficient light output and is ready for use. Remove the tester from the light wand prior to use in the surgical procedure.



If the colored circle does not appear on the black disk of the PowerCap light tester by the end of the complete light cycle, wait 2 minutes, then repeat test procedure. If the colored circle does not appear after the second light cycle, repeat the test procedure with a new light wand. If the test still fails, refer to the Troubleshooting section of the FocalSeal Light Source/Light Wand Operating Instructions.

Keep the PowerCap light tester available in the sterile field for additional intra-operative light output tests. Do not discard until procedure is complete.

FocalSeal-L Material Preparation:

Note: Allow 10 minutes for material preparation.

2.1 If the window on the indicator strip has turned completely blue, do not use. Discard the package and retrieve another frozen material set from the freezer.

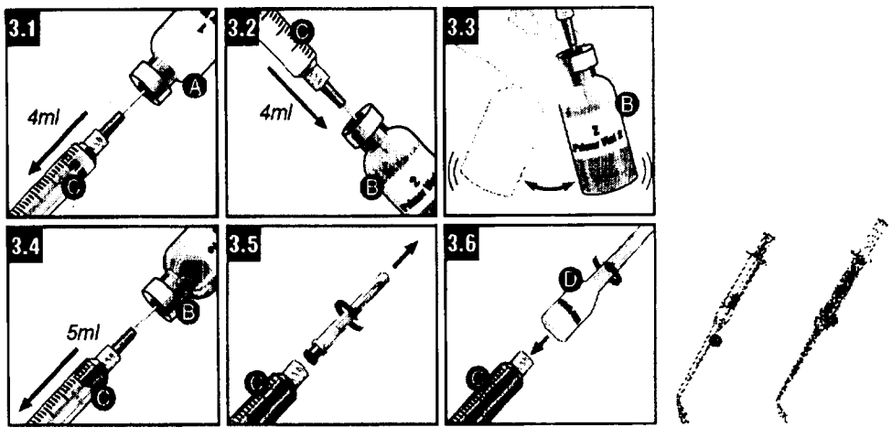
PRECAUTION:

- Do not thaw Primer Vial 2 in warm sterile saline.

FocalSeal-L Primer and Sealant Preparation:

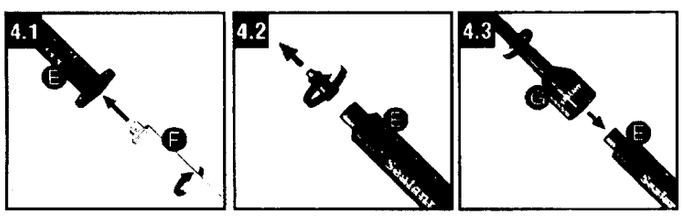
2.2 Thaw the FocalSeal-L Primer solution Vial 1 and the FocalSeal-L Sealant syringe. If Vial 1 is not thawed upon opening, place Primer Vial 1 into a pan filled with warm sterile saline. (Approximately 6 minutes in warm saline bath or approximately 45 minutes at room temperature).

Primer Preparation:



Note: The primer has a white applicator and the sealant has a black applicator. Take care to connect the proper applicator to the appropriate syringe.

Sealant Preparation:



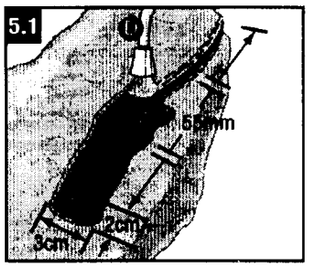
Target Site Preparation:

1. Prior to application of FocalSeal-L Sealant, ensure that the surgical procedure is complete and hemostasis has been achieved. 2. Rinse the area to be treated with saline and remove any pooled blood or blood clots with irrigation and/or suction. 3. Ventilation of the target area should be stopped. If patient needs to be ventilated, a reduced tidal volume is recommended to minimize lung movement and active air leakage during application.
4. Maximum area for single application of primer/sealant is 3 cm diameter or 55 mm linear staple line. For areas larger than this, apply in stages. Clean brushes with sterile saline between applications.

- **FocalSeal-L Sealant is contraindicated for application on oxidized regenerated cellulose and absorbable gelatin sponges, as adherence will be compromised.**

Note: If target site is vertical, allow suction to provide drainage at lowest point of target field, to ensure that primer or other fluids do not pool when sealant solution is being applied.

Primer Application:

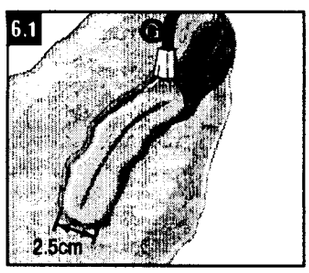


5.1 Apply primer solution sparingly through applicator while brushing the target surface. Ensure complete but thin distribution up to a minimum of 1 cm margin around the perimeter of the target site. Apply sufficient primer to coat the target site, while avoiding pooling and bubbling of primer material on the surface.

FocalSeal-L Surgical Sealant Application:

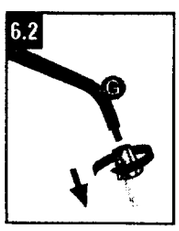
Note: If more than 30 seconds elapses between the application of primer and application of sealant, rinse treated area with saline and re-apply primer before applying sealant.

6.1 Apply a few drops of sealant through the applicator, then briefly brush the surface of the target tissue using the sealant applicator brush to spread sealant evenly and blend the sealant within primed area only.

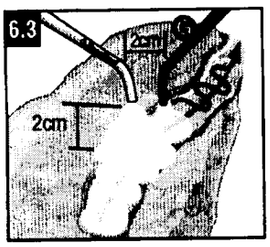


Note: The brush should be cleaned during the sealing cycle. Proper brush cleaning can be accomplished by removing any excess material, which might build up during the sealing cycle, using a dry or dampened gauze sponge. Repeat brush-cleaning steps as necessary between uses during the sealing process. Brush can be cleaned repeatedly in this manner without disturbing the brush and bristle integrity.

- Remove the sealant brush tip and apply sealant directly over the target site.



- Apply an uninterrupted layer of sealant, approximately 1 mm thick, in a continuous serpentine manner. Do not apply the sealant solution beyond the primed area. After the sealant has spread onto the target surface to form a thin laminating layer, expose the sealant to one complete 40-second light cycle using the Light Source/Light Wand. The tip of the Light Wand should be positioned perpendicular to and approximately 2 cm above the surface of the sealant.



PRECAUTION:

- Keep the light wand tip approximately 2 cm away from tissue surface so that sealant solution receives adequate light exposure, and application site can be polymerized in one light cycle.

Note: The activated light wand should follow the applicator as sealant solution is being dispensed, but not so closely that the sealant prematurely gels before it can spread. This can be accomplished by maintaining a distance of approximately 2 cm between the center of the illuminated area and the applicator tip.

- Bubbles may appear as end of sealant solution supply is reached. Avoid bubbles in sealant material during application in order to ensure maximum integrity of the sealant.
- Do not allow the light wand tip to contact tissue, tissue fluid, sealant solution or primer solution, as the residue from these materials may compromise the light output of the wand. If the tip becomes contaminated with a foreign substance, clean with sterile saline and wipe with dry gauze to maintain maximum light output.

7. If the target site is sealed in segments, repeat step 5.1 through 6.3 by allowing a minimal (0.5cm) overlap in application segments.

Re-application:

1. Visually inspect the area for full sealant coverage. If a site is not properly sealed, remove any detachable sealant material with sharp dissection, re-prime and apply sealant as outlined in step 5.1 through 6.3, in a slightly wider perimeter if necessary.
2. Ensure that no sutures or suture tails are sticking through the sealant material. If a suture protrudes and therefore is not properly covered, deposit enough sealant material only to cover the suture material. Alternatively, trim the tails to a shorter length, and reapply sealant.

Note: Primer is necessary only at tissue interface, and need not be used when depositing additional sealant to the initial sealant layer.