CryoLife, Inc.
Biotechnologies for Medicine℠

Proposed
BioGlue® Surgical Adhesive Instructions for Use

Table of Contents

DEVICE DESCRIPTION....2
INDICATIONS FOR USE....2
CONTRAINDICATIONS....2
WARNINGS....3
PRECAUTIONS....3
ADVERSE EVENTS – OBSERVED AND POTENTIAL INCIDENTS....4
Observed Adverse Events....4
Potential Adverse Events....5
CLINICAL STUDIES....5
HOW SUPPLIED....12
PATIENT COUNSELING INFORMATION....12
DIRECTIONS FOR USE....13
Delivery Device Preparation....13
Site Preparation and BioGlue Delivery Device Priming....13
General Techniques for the Use of Adhesive in Surgery....14
MAINTAINING DEVICE EFFECTIVENESS....15
Precautions....15
Cleaning....15
Sterilization....16
PRODUCT INFORMATION DISCLOSURE....16
DISCLAIMER OF IMPLIED WARRANTIES....16

CryoLife, Inc.
Biotechnologies for Medicine℠

BioGlue® Surgical Adhesive
Instructions for Use

Caution: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

Read Instructions for Use prior to using this product.

DEVICE DESCRIPTION

BioGlue Surgical Adhesive (BioGlue), manufactured by CryoLife, Inc., Kennesaw, GA, may be used prophylactically or after a leak is detected to seal and reinforce anastomoses in cardiac and vascular surgical repairs.

BioGlue is a two-component surgical adhesive composed of purified bovine serum albumin (BSA) and glutaraldehyde. The BSA is derived from serum obtained from cattle exclusively from bovine spongiform encephalopathy (BSE) free countries and undergoes processing that removes/inactivates viruses. The solutions are dispensed by a controlled delivery system, composed of a reusable delivery device, applicator tips, and applicator tip extenders. Once dispensed, the adhesive solutions (in a predefined ratio) are thoroughly mixed *in vitro* through the tortuous path of the applicator tip where cross-linking starts to occur. The glutaraldehyde molecules covalently bond (cross-link) the BSA molecules to each other and, upon application, to the tissue proteins at the anastomotic repair site thereby creating a flexible mechanical seal, independent of the body's clotting mechanism. The device-mediated application is designed to provide reproducible mixing of the components *in vitro* and higher bonding strength than manual on-site (*in situ*) mixing and application. BioGlue begins to set up within 20 to 30 seconds and reaches its bonding strength within 2 minutes. BioGlue also adheres to synthetic graft materials via mechanical interlocks within the interstices of the graft matrix.

INDICATIONS FOR USE

BioGlue® Surgical Adhesive is indicated for use as an adjunct to standard methods of cardiac and vascular repair such as sutures (or staples) to provide hemostasis.

CONTRAINDICATIONS

- Do not use in patients with known allergies to materials of bovine origin.
- Not for intravascular use.
- Not for cerebrovascular repair.

WARNINGS

- BioGlue Surgical Adhesive is not intended as a substitute for sutures or staples.
- Do not expose tissue to the device if it may be adversely affected by contact with the device, e.g., aortic valve cusps and intra-cardiac structures.
- Do not allow device in either the uncured or polymerized form to contact circulating blood flow.
- Avoid exposing any nerves to surgical adhesive.
- Avoid contact with skin or other tissue not intended for application.
- Glutaraldehyde treated tissue has an enhanced propensity for mineralization. Laboratory experiments indicate that unreacted glutaraldehyde may have mutagenic effects.
- Unreacted glutaraldehyde may cause irritation to eye, nose, throat, or skin; induce respiratory distress; and local tissue necrosis. Prolonged exposure to unreacted glutaraldehyde may cause a central nervous system or cardiac pathology. Operators using the device should ensure that staff are adequately risk protected.
- BioGlue should not be used in the presence of infection and should be used with caution in contaminated areas of the body.
- Exposure to bovine serum albumin may cause a reaction such as swelling or edema at the application site.
- BioGlue Surgical Adhesive contains a material of animal origin, which therefore may be capable of transmitting infectious agents.

PRECAUTIONS

- It is recommended that surgical gloves, sterile gauze pads/towels, and surgical instruments be maintained moist to minimize the potential for BioGlue inadvertently adhering to these surfaces.
- Wear gloves, mask, protective clothing, and safety glasses. If contact with solutions occurs, flush affected areas immediately with water and seek medical attention.
- BioGlue Surgical Adhesive solutions cartridges, applicator tips, and applicator tip extenders are for single patient use only. Do not re-sterilize.
- Do not use if packages have been opened or damaged.
- Do not prime delivery device until ready for immediate use. Premature priming may cause the applicator tip to become obstructed with polymerized adhesive.
- Take care not to spill solutions out of the cartridge.
- Do not compress the handle of the adhesive delivery device while attaching the cartridge to the delivery device.
- Attempting to apply the adhesive in a surgical field that is too wet may result in poor adherence.
- Ensure priming material does not come into contact with the surgical site.
- BioGlue Surgical Adhesive sets up immediately. Priming must occur quickly, followed immediately by the application of adhesive. Pausing between priming and application can cause set-up of adhesive within the applicator tip.
- If the BioGlue Surgical Adhesive adheres to an undesired location, allow the adhesive to polymerize and then attempt to gently dissect the adhesive away from the affected area with forceps and scissors. Do not attempt to peel away the BioGlue Surgical Adhesive as this could result in tissue damage at the application site.

ADVERSE EVENTS – OBSERVED AND POTENTIAL

Observed Adverse Events

In a prospective, multi-center, randomized controlled clinical trial, a total of 76 patients received standard surgical repair with BioGlue Surgical Adhesive and 75 received only standard surgical repair of cardiac and vascular anastomoses. Following is a complete list of adverse events that were observed in the BioGlue Surgical Adhesive group patients in the pivotal clinical trial.

Observed Adverse Events

Adverse Event Description	BioGlue Group N = 77			Control Group N = 74			P-Value
	n	%	#events	n	%	#events	
Application of Adhesive to Non-Targeted Tissue[1]	1	1.3%	1	0	0%	0	1.000
Death	5	6.5%	5	5	6.8%	5	0.999
Failure of Products to Adhere to Tissue[1]	1	1.3%	1	0	0%	0	1.000
Hemorrhage	3	3.9%	3	3	4.1%	3	1.000
Infection	13	16.9%	15	10	13.5%	13	0.653
Inflammatory, Immune Systemic Allergic Reaction[2]	2	2.6%	2	0	0%	0	0.497
Irreversible Morbidity	0	0%	0	1	1.4%	1	0.490
Ischemia	3	3.9%	3	2	2.7%	2	1.000
Myocardial Infarction	3	3.9%	3	1	1.4%	1	0.620
Neurological Deficits	5	6.5%	6	16	21.6%	18	0.009
Organ System Dysfunction/Failure	3	3.9%	4	2	2.7%	2	1.000
Paraplegia	1	1.3%	3	2	2.7%	3	0.615
Pleural Effusion	20	26.0%	25	21	28.4%	22	0.855
Renal Dysfunction/Failure	13	16.9%	13	9	12.2%	10	0.492
Respiratory Dysfunction/Failure	13	16.9%	18	12	16.2%	15	1.000
Stroke or Cerebral Infarction	1	1.3%	1	3	4.1%	5	0.360
Thromboembolism	1	1.3%	1	1	1.4%	4	1.000
Thrombosis	0	0%	0	1	1.4%	1	0.490
Other[3,4]	46	59.7%	108	40	54.1%	100	0.514

[1] These adverse events were device related. Both complications were clearly warned against in the IFU.

[2] These adverse events were not device related. One patient had an allergic reaction to a preoperative antibiotic and the other patient hadan allergic reaction to Protamine.

[3] Other adverse events observed in the BioGlue treated clinical trial patients were as follows: Acidosis (1%), Acute shortness of breath (1%), Altered mental status (3%), Anemia (5%), Atelectasis (8%), Cardiac arrhythmia (22%), Cerebral hemorrhage (1%), Colecystitis (1%), Coagulopathy (1%), Congestive Heart Failure (4%), Decreased femoral pulse (1%), Deep Vein Thrombosis (1%), Depression (4%), Diarrhea (3%), Dysphagia (5%), Edema (3%), Fever (3%), Heart enlargement (4%), Hematuria (1%), Hemoptysis (1%), Hernia (4%), Hoarseness (1%), Hypotension (1%), Ileus (4%), Incisional pain (3%), Lymphatic fistula (1%), Malnutrition (5%), Nausea (3%), Perforatedviscus (1%), Pericardial effusion (1%), Pneumothorax (3%), Rectal bleeding (1%), Seizure (1%), Thigh and back pain (3%), Thrombocytopenia (1%), Urinary retention (4%), Vocal cord paralysis (3%).

[4] Other adverse events observed in the Control Group clinical trial patients were as follows: Abdominal pain (1%), Abnormal lab value (5%), Acidosis (1%), Altered mental status (3%), Anemia (3%), Angina (1%), Aphasia (1%), Atelectasis (4%), Back pain (1%), Cardiac arrhythmia (19%), Cerebral hemorrhage (3%), Congestive heart failure (1%), Diarrhea (3%), Dizziness (1%), Duodenal ulcer (1%), Dysphagia (1%), Edema (1%), Emphysema (1%), Encephalopathy (1%), Failed extubation (1%), Fever (3%), Heart block (2%), Hematuria (1%), Hemothorax (1%), Hernia (1%), Hoarseness (4%), Hypotension (4%), Ileus (3%), Incisional pain (5%), Lower extremity weakness (1%), Nausea (4%), Near syncope (1%), Neck deformity (1%), Pericardial effusion (3%), Pneumothorax (3%), Post-kidney collection (3%), Reintubation (1%), Seizure (1%), Sexual dysfunction (1%), Shortness of breath (1%), Thrombocytopenia (4%), Thrombophlebitis (1%), Transfusion reaction (3%), Urinary retention (1%), Valve surgery (1%), Vocal cord paralysis (3%).

Adverse events were equal in severity in both the BioGlue group and the standard surgical repair group. There were no unanticipated device effects (UADE) in this investigation.

Potential Adverse Events Related to Cardiac and Vascular Procedures

Adverse events associated with cardiac and vascular repair procedures may include but are not limited to:

- Cardiac tamponade
- Infection
- Hemorrhage
- Paraplegia
- Dissection
- Ischemia
- Adhesions
- Injury to normal vessels or tissue
- Thrombosis
- Vasospasm
- Vessel rupture and hemorrhage
- Pleural effusion
- Pulmonary emboli
- Renal dysfunction/failure
- Aortic insufficiency
- Myocardial infarction
- Neurological deficits
- Cerebral emboli
- Stroke or cerebral infarction
- Anastomotic pseudoaneurysm
- Respiratory dysfunction/failure
- Organ system dysfunction/failure
- Death or irreversible morbidity

CLINICAL STUDIES

In June 1998, CryoLife, Inc. began a clinical trial investigating the use of BioGlue as an adjunct in the surgical repair of acute, Stanford Type A aortic dissections. CryoLife filed a Humanitarian Device Exemption (HDE) for the use of BioGlue in the surgical repair of acute thoracic aortic dissections, which was approved by FDA in December 1999 (H990007). The data is suggestive of a benefit in terms of 1) decreased rate of reoperation for bleeding and other bleeding complications without the need for other hemostatic devices and/or pharmacological agents, 2) fewer intraoperative blood transfusions, and 3) reinforcement of friable tissue of the dissected aorta without the need for pledgets. CryoLife gained approval in May 2000 to investigate the use of BioGlue for sealing anastomotic sites in cardiac and vascular repairs. Following is information from the cardiac and vascular repair investigation:

Study Design

The "BioGlue Surgical Adhesive Effectiveness and Safety Trial as a Surgical Adjunct in Cardiac and Vascular Surgical Repairs ("BEST" Trial) was a prospective, multi-center, randomized controlled trial. Randomized cardiac and vascular repairs include an adjunctive BioGlue prophylactic treatment and a control group (standard surgical repair). The overall objective was to collect clinical data concerning the safety and effectiveness of BioGlue used as an anastomotic sealant to provide hemostasis.

Cardiac and vascular repair procedures included but were not limited to the surgical repair/reconstruction of the following clinical conditions: ventricular aneurysm/rupture; aortic

aneurysm/dilatation (root, ascending arch, descending thoracic, thoracoabdominal, abdominal, and aortoiliac); traumatic aortic transection; annulo-aortic ectasia; and vascular bypass or repair.

Patients were randomized to receive standard surgical repair with BioGlue applied to the anastomotic site (BioGlue group) or standard surgical anastomotic repair alone (control group).

Patient Assessment

Effectiveness Evaluations

The BioGlue group and the standard surgical repair group were compared to determine BioGlue's effectiveness for the following endpoints:

Primary Evaluation

Anastomotic hemostasis (yes or no) of each of the repaired anastomotic sites. Anastomotic hemostasis was defined as an anastomosis that does not require additional agents (pledgets, sutures, hemostatic devices, antifibrinolytic agents, thrombin glues, fibrin glues) at the treated site(s) to control bleeding at any point during the course of the original operation. Results were also evaluated on a "per patient" basis. Patients with anastomotic hemostatis at all anastomotic sites were considered successful.

Secondary Evaluations

- Quantity, type, and number of donor exposures of blood replacement products administered.
- Type of additional agents used (pledgets, sutures, hemostatic devices, antifibrinolytic agents, thrombin glues, fibrin glues)
- Re-operation due to anastomotic site bleeding.
- Major complications/adverse events through final follow-up.
- Minor complications/adverse events through final follow-up.
- Early hospital discharge mortality and mortality through last follow-up.

Cost Benefit Evaluations

- Total cardiopulmonary bypass time (when applicable).
- Time required for aortic cross-clamp (when applicable).
- Total operative time (skin incision to skin closure).
- Total time in Intensive Care Unit.
- Total hospitalization time.

Safety Evaluations

The criteria for evaluating safety in this patient population were:

- Unanticipated Adverse Device Effects (UADE).
- Device complications.
- Surgical procedure complications.

Demographic Data

A total of 151 patients were treated at 6 investigational sites in the cardiac and vascular repair arm of the U.S. IDE clinical trial. Pertinent information about the patient population is presented in Tables 2 and 3. Surgical procedures performed are shown in Table 4.

Table 2 – Summary of Subjects

	Treatment Group		
Population	**Surgical Repair with BioGlue**	**Conventional Surgical Repair**	**Total**
All Randomized	76	75	151
Cross Over	N/A	1	1
Intent-to-Treat	76	74	150
Evaluable	76	74	149
Safety	77	74	151

Table 3 – Demographic Characteristics (*All randomized patients)*

	Treatment Group			
Characteristic	**Surgical Repair with BioGlue**	**Conventional Surgical Repair**	**Crossover**	**Total**
Age (years)				
N	76	74	1	151
Mean (SD)	63.4 (17.2)	66.3 (12.7)	73.8 (N/A)	64.8 (15.1)
Min, Max	21, 87	25, 86	N/A	20, 87
Gender				
Male	49	48	0	97
Female	27	26	1	54
Total	76	74	1	151
Race				
African-American	6	6	0	12
Asian	1	1	0	2
Caucasian	67	66	1	133
Hispanic	2	1	0	3
Total	76	74	1	151

Table 4 – Cardiac and Vascular Procedures Included

	Treatment Group			
System	**Surgical Repair with BioGlue**	**Conventional Surgical Repair**	**Crossover**	**Total**
Cardiac Procedures**	24	25	0	49
Aortic Procedures†	57	47	1	105
Peripheral Vascular Procedures***	25	23	0	48
Total	106	95	1	202

***Cardiac repairs include: aortic root replacements (4), aortoplasty (1), aortic valve annuloplasty (5), aortic valve resuspension (1), aortic valve replacement (23), Bentall procedure (2), composite valved conduit procedures (8), mitral valve replacements (2), Ross procedure (2), coronary artery bypass grafting (1).*

†*Aortic aneurysm repairs include: abdominal aortic aneurysm (21), ascending aortic aneurysm (21), ascending/ transverse aortic arch aneurysm (9), ascending/ transverse arch/ descending aortic aneurysm (1), descending aortic aneurysm (8), thoracoabdominal aortic aneurysm (32), transverse aortic arch aneurysm (12), Type B aortic dissection (1)*

****Peripheral vascular repairs include: aorto-femoral bypass (5), aorto-iliac bypass (2), aorto-innominate bypass (1), carotid bypass (1), carotid endarterectomy (19), femoral-distal bypass (3), femoral-femoral bypass (2), femoral-popliteal bypass (5), hepatic-renal bypass (1), popliteal-dorsalis pedis bypass (1), profunda endarterectomy (1), renal bypass (6), renal endarterectomy (1)*

Data Analysis and Results

The tables and figures in this section present information from the cardiac and vascular repair arm of the U.S. IDE clinical trial.

Efficacy Data

Table 5 presents the intra-operative hemostasis data for the intent-to-treat patients on both a "per patient" and a "per anastomotic repair site" basis. The proportion of both patients and anastomotic repair sites achieving hemostasis based upon the protocol definition was statistically greater in the BioGlue group (Fisher's Exact Test, $p < 0.05$).

Table 5 – Intra-operative Hemostasis – Intent-to-Treat Patients (Success/Total)

	Treatment Group		
	Surgical Repair With BioGlue	Conventional Surgical Repair	P value
Per patient*	61% (46/76)	39% (29/74)	0.014
Per Repair Site**	81% (164/202)	57% (105/184)	<0.001

* Hemostasis on a "per patient" basis was defined as hemostasis of 100% of the anastomotic repair sites.

** The average number of repair sites (anastomoses) per patient were 2.6 (range: 1 to 8).

Use of intra-operative blood products is outlined in Table 6. No statistically significant differences were noted between the BioGlue group and the control group based upon a one-sided 95% confidence interval of the difference between the treatment means.

Table 6 –Intra-operative Blood Products and Donor Exposures *(Intent-to-Treat Patients)*

	Treatment Group	
	Surgical Repair With BioGlue	Conventional Surgical Repair
Red Blood Cells		
N	76	74
Mean (SD)	2.3 (3.6)	1.9 (2.4)
Min, Max	0, 22	0, 12
Platelets		
N	76	74
Mean (SD)	5.1 (10.1)	5.2 (10.0)
Min, Max	0, 60	0, 50
Fresh Frozen Plasma		
N	75	73
Mean (SD)	3.8 (6.6)	3.3 (5.0)
Min, Max	0, 30	0, 19
Cryoprecipitate		
N	74	72
Mean (SD)	4.3 (11.9)	2.0 (8.3)
Min, Max	0, 60	0, 40
Total Number of Donor Exposures		
N	48	51
Mean (SD)	20.6 (26.3)	14.2 (18.2)
Min, Max	0, 106	0, 89

Investigators in this trial documented their usage of pledgeted sutures to reinforce their primary repair. Anastomotic sites treated with BioGlue had a statistically lower incidence of pledget usage on the primary repair when compared to the control group (Table 7).

Table 7 – Pledgets on Primary Repair - Intent-to-Treat Anastomotic Sites (Success/Total Number of Anastomotic Sites)

	Treatment Group		
	Surgical Repair with BioGlue	Conventional Surgical Repair	P Value
Pledgets Used on Primary Repair	26% (53/202)	36% (66/184)	0.047

Any anastomotic repair site that was not immediately hemostatic was evaluated to determine the additional methods used to obtain hemostasis. There was no statistical difference noted in the additional measures taken to obtain hemostasis, which indicates that BioGlue did not inhibit the surgeons ability to obtain hemostasis through use of conventional measures or additional BioGlue. These results are summarized in Table 8 below:

Table 8 – Measures Required to Obtain Hemostasis - Intent-to-Treat Bleeding Anastomotic Sites (Bleeding Anastomotic Sites Requiring Measure/Total Bleeding Sites)

	Treatment Group		
	Surgical Repair With BioGlue	Conventional Surgical Repair	P value
Make-up Stitches	82% (31/38)	81% (64/79)	1.00
Hemostatic Device*	8% (3/38)	10% (8/79)	1.00
Additional BioGlue	55% (21/38)	N/A	N/A
Other†	8% (3/38)	19% (15/79)	0.17

* *Hemostatic Devices included Surgicel®, Avitene®, Gelfoam®, Fibrin Glue, Thrombin Glue.*

† *Other includes: Additional pledgets (16), FloSeal (1), Teflon felt ring (1)*

The study protocol allowed investigators to "cross-over" and use BioGlue for control patients who suffered uncontrollable bleeding. Only one patient was noted to have uncontrollable bleeding. The investigator was able to obtain hemostasis at all anastomotic sites after using BioGlue for this patient.

Incidence of re-operation for anastomotic site bleeding is presented in Table 9. Only one patient had a re-operation due to anastomotic site bleeding.

Table 9 – Re-operation Due to Anastomotic Site Bleeding

	Treatment Group		
	Surgical Repair With BioGlue N (%)	Conventional Surgical Repair N (%)	One-Sided 95% Confidence Interval
Re-operation	0 (0.0%)	1 (1.4%)	[--, 0.9]

Table 10 shows a summary of intra-operative times, days spent in the ICU, and total hospitalization time. The differences between the BioGlue group and the control group were not statistically significant.

Table 10 – Procedure, ICU, and Hospitalization Times
(Intent-to-Treat)

	Treatment Group	
	Surgical Repair With BioGlue	Conventional Surgical Repair
Procedure Times		
Cardiopulmonary Bypass Time* (minutes)		
N	34	35
Mean (SD)	168.1 (67.4)	144.2 (60.6)
Min, Max	54, 358	54, 387
Cross-Clamp Time* (minutes)		
N	54	55
Mean (SD)	74.0 (46.1)	69.1 (41.3)
Min, Max	10, 196	19, 196
Total Operative Time (minutes)		
N	75	73
Mean (SD)	237.7 (125.1)	228.7 (100.8)
Min, Max	85, 650	60, 515
ICU Time		
Days in ICU*		
N	70	72
Mean (SD)	3.9 (5.6)	4.8 (7.1)
Min, Max	0, 32	0, 36
Hospitalization Time		
Days in Hospital		
N	72	73
Mean (SD)	9.5 (10.6)	10.9 (9.7)
Min, Max	1, 81	1, 55

* *Where applicable.*

Safety Data

Mortality rates for intent-to-treat in this trial are presented in Table 11. No differences were observed in either early (through hospital discharge) mortality or late (through final follow-up) mortality.

Table 11 – Mortality Rates – Intent-to-Treat Patients (Event/Total)

	Treatment Group		
	Surgical Repair With BioGlue	Conventional Surgical Repair	One-Sided 95% Confidence Interval
Early/Hospital Discharge (<30 days)	3.9% (3/76)	2.7% (2/74)	[--, 6.1]
Post-operative Follow-up (3 months)	1.3% (1/76)	4.1% (3/74)	[--, 3.9]

Adverse events were equal in severity in both the BioGlue group and the standard surgical repair group. There were no unanticipated device effects (UADE) in this investigation.

Conclusion

BioGlue was noted to have a statistically higher rate of intra-operative hemostasis when compared to the control group on both a "per patient" and a "per anastomotic site" basis. BioGlue-treated patients demonstrated a lower incidence of adjunctive pledgets use on their primary repairs to achieve hemostasis. There were no statistical differences in other endpoints, such as blood products or operative times, between study and control patients.

HOW SUPPLIED

The adhesive solutions cartridge, applicator tips, and twist rings are supplied sterile for single-patient use only. Discard unused material from opened or damaged product.

The adhesive solutions are contained within a capped, double-chambered cartridge. The cured adhesive is non-pyrogenic. Store below 25°C, but do not freeze.

The Delivery Device is supplied sterile. It may be resterilized and reused nine times. Refer to section "Reusable Delivery Device Product Reuse Instructions" of this package insert for detailed cleaning and resterilization instructions. Retain these Instructions for Use for future reference.

PATIENT COUNSELING INFORMATION

Exposure to bovine serum albumin may cause a reaction such as swelling or edema at the application site.

BioGlue Surgical Adhesive contains a material of animal origin, which therefore may be capable of transmitting infectious agents.

DIRECTIONS FOR USE

Delivery Device Preparation

1. Remove a sterile solutions cartridge from its package. Firmly grasp the cartridge with the nose facing upward. Turn the twist-off cap 90° counterclockwise and gently remove from the solutions cartridge by rocking it side to side.

   CAUTION: Take care not to spill solutions out of cartridge during assembly.

2. Remove a sterile applicator tip from package.
3. While holding the cartridge with one hand, place the applicator tip on the cartridge. Take care to align notches on the collar of the applicator tip with the notches of the cartridge nose.
4. If using a twist ring tool, remove it from its packaging, place it over the applicator tip and slide it firmly onto the applicator tip's rotating collar. Holding the twist ring tool or applicator tip collar, push the applicator tip down firmly onto the cartridge and then rotate the collar 90° clockwise to lock tip in place.
5. If used, remove the twist ring tool and keep it for tip removal or any additional applicator tip exchanges that may take place during the procedure.
6. Remove the adhesive delivery device trigger assembly (handle) and dual head plunger (plunger) from package. Lift the large latch (cartridge retainer latch) on top of the handle. While pushing upward on the small latch (plunger latch) located on the back of the handle, insert the plunger (with the ribbed surface facing downward) into the slit located at the front of the device. Still holding the plunger latch upward, push the plunger back completely. Align the small and large barrels of the solutions cartridge above the corresponding small and large plunger heads. Slide the solutions cartridge down into position and push cartridge retainer latch down to lock.

   CAUTION: Do not compress the handle of the adhesive delivery device while attaching the cartridge to the delivery device.

7. Gently slide the plunger forward into position until resistance is felt. The assembled adhesive delivery device is now ready for priming and immediate use.
8. If using an applicator tip with flexible extension, a desired angle may be created by bending the tip at the appropriate location and holding for 3-5 seconds. The angle created should hold for 5 minutes.
9. To remove the solutions cartridge, push and hold plunger latch upward while completely drawing back the plunger. Lift the cartridge retainer latch and slide the solutions cartridge out.
10. To remove occluded applicator tips, hold the applicator tip collar, rotate 90° counter-clockwise, and gently lift the applicator tip off of the solutions cartridge by rocking it side to side. The twist ring tool may be used to aid in turning the applicator tip collar.

Site Preparation and BioGlue Delivery Device Priming

1. Completely prepare the surgical site for adhesive application prior to priming or dispensing of the adhesive. A dry field will maximize adhesive contact with tissue. An optimal dry field can be described as a surgical site that does not restain with blood within 4-5 seconds after drying.

   CAUTION: Attempting to apply the adhesive in a surgical field that is too wet may result in poor attachment.

2. Prime immediately prior to application by compressing the device trigger, expelling a narrow ribbon of adhesive approximately 3 cm long onto a disposable surface (i.e., gauze, towel, or sample cup).

   CAUTION: Ensure priming material does not come into contact with the surgical site.

3. If the primed material looks colorless or contains bubbles, it could indicate that the first compression of the device trigger resulted in inadequate mixing. Repeat the prime until the mixture is a homogeneous light yellow to amber colored liquid. A properly primed device will deliver a uniform liquid with no bubbles.
4. Quickly proceed to application.

   CAUTION: BioGlue Surgical Adhesive sets up immediately. Priming must occur quickly, followed immediately by the application of adhesive. Pausing between priming and application can cause set-up of adhesive within the applicator tip.

General Techniques for the Use of Adhesive in Surgery

Before using the BioGlue Surgical Adhesive, surgeons should become familiar by appropriate training with the surgical techniques and variations. The use of BioGlue Surgical Adhesive should be practiced prior to initial use in the surgical suite.

1. The patient should be prepared and draped according to the site's standard procedures. Procedures such as entry of the chest, cardiopulmonary bypass, clamping, and myocardial protection should follow the surgeon's standard techniques.
2. Maintain a dry surgical field during the application of the adhesive. An optimal dry field could be described as a surgical site that does not restain with blood within 4-5 seconds after removal.
3. The tissue surrounding the surgical site can be protected from the undesired application of BioGlue Surgical Adhesive by placing moist sterile gauze pads in these areas. Directly after application, remove gauze before adhesive polymerizes.
4. If BioGlue Surgical Adhesive does adhere in an undesired location, allow the adhesive to polymerize and then attempt to gently dissect the adhesive away from the affected area with forceps and scissors.

   CAUTION: Do not attempt to peel away the BioGlue Surgical Adhesive as this could result in tissue damage at the application site.

5. Apply an even adhesive coating 1.2 - 3.0 mm thick for anastomosis of vessels with greater than 2.5 cm diameter or tissue reinforcement; apply an even adhesive coating 0.5 - 1.0 mm for vessels with less than 2.5 cm diameter.
6. Do not compress the area of application or subject it to extra pressure. Allow the adhesive to polymerize for at least 2 minutes. Once the adhesive has polymerized (wait at least 2 minutes), remove the sponges or balloon catheter from within the lumen and secure sutures as necessary.

7. After adhesive hardens, trim away excess or irregular adhesive edges with scissors and pickups.

   CAUTION: If the BioGlue Surgical Adhesive adheres to an undesired location, allow the adhesive to polymerize and then attempt to gently dissect the adhesive away from the affected area with forceps and scissors. Do not attempt to peel away the BioGlue Surgical Adhesive as this could result in tissue damage at the application site.

8. If a portion of the dissected/repaired vessel or tissue is replaced with a graft, potential bleeding sites at the anastomosis between the graft and the native tissue can be sealed with BioGlue Surgical Adhesive. The field must be dry and free of blood.

MAINTAINING DEVICE EFFECTIVENESS

Precautions

1. Do not use glutaraldehyde based cleaners or other cleaners corrosive to metal parts as these may corrode parts of the delivery device and impede its function.
2. Do not use ultrasonic cleaning methods as these may lead to material fatigue and to failure of the device.
3. Do not use dry heat cleaning methods as this device is not designed to withstand these high temperatures.
4. Do not clean with enzyme-based detergents since these may reduce the number of times the delivery device may be reused.

Cleaning

Inspect the adhesive delivery device for signs of deterioration or damage such as cracking, blistering, or pitting. Discard if deterioration or damage is observed. Remove the plunger from the handle by lifting the plunger latch upward and drawing forward the plunger. CryoLife has determined that the adhesive delivery device may be satisfactorily cleaned by thoroughly washing with a mild detergent such as Alconox®. The effectiveness of other cleaning solutions has not been determined.

NOTE: Use of the Alconox® trademark in this document does not constitute an endorsement by CryoLife, Inc. Alconox® is listed only as an example.

Sterilization

Sterilize by autoclaving. The BioGlue Delivery Device should first be cleaned and placed in appropriate packing materials. The following autoclave settings have been tested to ensure sterility and product functionality:

Cycle Temperature (C)	Cycle Temperature (F)	Cycle Time	Cycle Type
121 – 131°C	250 – 268°F	30 minutes	Pre-vacuum
132°C	270°F	4 - 30 minutes	Pre-vacuum
134°C	273°F	3 - 18 minutes	Pre-vacuum
132°C	270°F	10 minutes	Gravity

Exposures outside of these settings have not been evaluated. The BioGlue Delivery Device can be resterilized up to 9 times under normal use.

NOTE: The user should verify that the BioGlue Delivery Device is still functional after each cleaning and sterilization. This is easily accomplished by assembling the BioGlue Delivery Device (described above) and observing that the plunger moves forward with each depression of the lever.

PRODUCT INFORMATION DISCLOSURE

Handling and storage of this device by the user as well as factors related to the patient, the patient's diagnosis, treatment, surgical procedures, and other matters beyond manufacturer's control may directly or indirectly affect this device and the results obtained from its use. This device should not be used except on the order of a physician.

DISCLAIMER OF IMPLIED WARRANTIES

CryoLife, Inc. disclaims all implied warranties with respect to this surgical adhesive, including but not limited to, the implied warranty of merchantability and any warranty of fitness for a particular purpose. Prices, specifications, and availability are subject to change without notice.

CryoLife, Inc.
Biotechnologies for Medicine℠

1655 Roberts Blvd., NW
Kennesaw, Georgia 30144 USA
770-419-3355 or 800-438-8285
Fax 770-590-3749