Summary of Safety and Effectiveness
CryoLife, Inc., BioGlue® Surgical Adhesive

1 General Information

Device Generic Name:.....Surgical Adhesive

Device Trade Name:.....BioGlue® Surgical Adhesive

Applicant's Name and Address:.....CryoLife, Inc.
1655 Roberts Boulevard, NW
Kennesaw, Georgia 30144

Premarket Approval (PMA) Number:.....P010003

Date of PMA:.....January 31, 2001

Date of PMA Preapproval Inspection:.....April 16-26, 2001

Date of Panel Recommendation:.....September 11, 2001

Date of Notice of Approval to Applicant:.....

2 Indications for Use

BioGlue® Surgical Adhesive is indicated for use as an adjunct to standard methods of achieving hemostasis (such as sutures and staples) in adult patients in open surgical repair of large vessels (such as aorta, femoral, and carotid arteries).

3 Device Description

BioGlue® Surgical Adhesive (BioGlue) is a two-component surgical adhesive composed of purified bovine serum albumin (BSA) and glutaraldehyde. The BSA is obtained from cattle exclusively from bovine spongiform encephalopathy (BSE) free countries and undergoes processing that reduces or 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 pre-defined ratio) are mixed in the applicator tip where cross-linking begins. The glutaraldehyde molecules covalently bond (cross-link) the BSA molecules to each other and, upon application, to the tissue proteins at the repair site, creating a flexible mechanical seal independently of the body's clotting mechanism. The delivery device-mediated application is designed to provide reproducible mixing of the components *in vitro*. BioGlue begins to polymerize 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. The BioGlue component has a shelf life of 3 years if stored at 25 °C.

4 Contraindications, Warnings and Precautions

4.1 Contraindications

- Not for patients with a known sensitivity to materials of bovine origin
- Not for intravascular use
- Not for cerebrovascular repair

4.2 Warnings

Warning: Animal studies have shown that direct application of BioGlue to the exposed phrenic nerve can cause acute nerve injury. BioGlue application to the surface of the heart can cause coagulation necrosis that extends into the myocardium, which could reach underlying conduction tissue and may cause acute, focal sinoatrial node degeneration.

- Do not use BioGlue as a substitute for sutures or staples.
- Do not expose valve leaflets or intracardiac structures to BioGlue.
- Do not allow BioGlue in either the uncured or polymerized form to contact circulating blood. BioGlue entering the circulation can result in local or embolic vascular obstruction.
- Avoid exposing nerves to BioGlue.
- Avoid contact with skin or other tissue not intended for application.
- Minimize use of BioGlue in patients with abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism). Glutaraldehyde-treated tissue has an enhanced propensity for mineralization. Laboratory experiments indicate that unreacted glutaraldehyde may have mutagenic effects.
- Do not use BioGlue if staff are not adequately protected (e.g. wearing gloves, mask, protective clothing, and safety glasses). Unreacted glutaraldehyde may cause irritation to eye, nose, throat, or skin; induce respiratory distress; and cause local tissue necrosis. Prolonged exposure to unreacted glutaraldehyde may cause a central nervous system or cardiac pathology. If contact occurs, flush affected areas immediately with water and seek medical attention.
- Do not use BioGlue in the presence of infection and use with caution in contaminated areas of the body.
- Avoid repeat exposure of BioGlue in the same patient. Hypersensitivity reactions are possible upon exposure to BioGlue. Sensitization has been observed in animals.
- BioGlue contains a material of animal origin which may be capable of transmitting infectious agents.

4.3 Precautions

- Safety and effectiveness of the BioGlue in minimally invasive procedures have not been established.
- Safety and effectiveness of the BioGlue in coronary artery bypass grafting (CABG) and other use on small diameter vessels has not been established.
- Do not use blood saving devices when suctioning excess BioGlue from the surgical field.
- 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.
- BioGlue 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.
- Take care not to spill contents of the solutions cartridge.
- Do not compress the main delivery unit trigger mechanism while attaching the solutions cartridge to the delivery device.
- Do not apply BioGlue in a surgical field that is too wet. This may result in poor adherence.
- Avoid tissue contact with material expelled from applicator during priming.
- BioGlue polymerizes rapidly. Priming must occur quickly, followed immediately by the application of BioGlue. Pausing between priming and application can cause polymerization within the applicator tip.
- Do not peel away BioGlue from an unintended site, as this could result in tissue damage.

5 Alternative Practices and Procedures

Conventional procedures used to control bleeding include the use of direct pressure, sutures, pledgets, and/or electrocautery. Absorbable hemostatic agents such as bovine gelatin powder and sponges, and hemostatic agents made from bovine collagen and oxidized cellulose are also used for stopping bleeding. Additionally products containing thrombin and/or fibrinogen are used to assist the body's natural clotting mechanism to achieve hemostasis.

6 Marketing History

BioGlue was approved in the United States for use in the repair of acute thoracic aortic dissection under the Humanitarian Device Exemptions (HDE) regulations (H990007) in December 1999 and has been marketed in the U.S. since that time. Commercial distribution of the device outside of the U.S. started in April 1998. BioGlue has not been withdrawn from marketing for any reason relating to safety or effectiveness of the device.

7 Potential and Observed Adverse Effects of the Device on Health

Observed Adverse Events

Adverse events observed during the clinical studies included the following (see Table 3 for more detail):

- BioGlue applied to non-targeted tissue
- Failure of BioGlue to adhere
- Death
- Hemorrhage
- Infection
- Inflammatory, immune systemic allergic reaction
- Irreversible morbidity
- Ischemia
- Myocardial infarction
- Neurological deficit
- Organ system failure
- Paraplegia
- Pleural effusion
- Renal dysfunction/failure
- Respiratory dysfunction/failure
- Stroke or cerebral infarction
- Thromboembolism
- Thrombus

Potential adverse events that may occur from the use of BioGlue

- A hypersensitivity reaction such as swelling or edema at the application site
- Application of adhesive to tissue not targeted for procedure
- Failure of BioGlue to adhere to tissue
- Local tissue necrosis
- Mineralization of tissue
- Possible transmission of infectious agents from material of animal origin
- Thrombosis and thromboembolism

Potential Adverse Events Related to Cardiac and Vascular Procedures

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

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

8 Summary of Preclinical Studies

8.1 Laboratory Studies

8.1.1 Biocompatibility

CryoLife conducted biocompatibility testing of the cured BioGlue implant material and all delivery system materials contacting the patient or adhesive solutions in accordance with Good Laboratory Practices. All of the irradiated materials that come in contact with the BioGlue adhesive solutions during storage were also assessed for extractable. The following table (Table 1) summarizes testing done on the cured BioGlue implant.

Table 1 – Biocompatibility Testing Results – Cured BioGlue Implant

Test Performed	Extract(s)	Test and Control(s)	Results/Comments
Cytotoxicity (ISO)	MEM	Natural rubber (+) Silicon tubing (-)	L-929 cells gave a grade 2-3 (mild-moderate) reactivity score with test extract at 48 hours
Sensitization (Maximization)	Saline and CSO	Saline and CSO (-) DNCB (+) with and without activation	No sensitization was observed
Intracutaneous Toxicity (ISO/USP)	Saline and CSO	Saline and CSO (-)	No toxicity observed in either extract
Systemic Toxicity (ISO/USP)	Saline (IV) and CSO (IP)	Saline and CSO	No signs of toxicity
Genotoxicity (Ames)	Saline	Saline (-) 2-aminoanthracene (+) sodium azide (+) 2-Nitrofluorene (+) 9-aminoacridine (+) with and without activation	No genotoxicity in TA98, TA100, TA1535, and TA1537 strains of *S. typhimurium*
Hemolysis (DHEW)	Saline	Saline (-) Water (+)	4.45% hemolysis, considered to be non-hemolytic
Rabbit pyrogen (ISO)	Saline	Saline (-)	<0.5 °C rise in all rabbits non-pyrogenic

Biocompatibility tests conducted on the applicator tip and solutions cartridge components included cytotoxicity, systemic and intracutaneous toxicity, sensitization, and pyrogenicity. All test results were “pass” or “non-toxic”. There was also data in the file regarding the applicator tip connector extenders and extender tubing. These passed the cytotoxicity, sensitization, irritation/intracutaneous toxicity, and systemic toxicity tests.

CryoLife also evaluated BioGlue implant tissue response as part of several animal implant studies to evaluate its safety and effectiveness (see section 8.2 Animal Studies). The observations of inflammation, necrosis, calcification and fibrosis in the BioGlue-treated groups were found to be consistent with a normal foreign body reaction. In humans, there has not been a chronic inflammatory response noted out to 9 months.

8.1.2 Analytical and Functional Testing

Analytical and functional testing is conducted on each lot of BioGlue to ensure that it meets established product specifications designed to ensure the device is safe for its intended use. Analytical tests include: UV-Vis Spectrophotometric Profile of BSA, pH Determination of BSA Solutions, Monomeric Content of BSA by SDS-PAGE, Protein Concentration of BSA Solutions by Colorimetric Assay, Glutaraldehyde Concentration Determination by Hydroxylamine-HCl Titration, and Extent of Autopolymerization of Glutaraldehyde by Absorbance Ratio. Functional tests include Adhesive Cure Rate and Adhesive Shear. The device possesses adequate bonding strength and is reproducible in its chemical characteristics.

8.2 Animal Studies

8.2.1 Surgical Repair of Aortic Dissections in Sheep

A three-month study to determine the effects of BioGlue in the surgical repair of aortic dissection in sheep was conducted to evaluate device performance. A descending aortic dissection was created in sheep[1], using the following criteria: false lumen volume <50% of the total aortic volume, length of < 7.1 cm and width < 2.6 cm. Dissections that did not meet these criteria were considered unstable for repair. Animals with acceptable dissections were then randomized in a blinded fashion to surgical repair of the proximal flap alone, or repair by gluing the layers of the dissection together with BioGlue and surgical repair of the Proximal flap. There were 26 aortic dissections that met the acceptance criteria, with 13 animals randomized to surgical repair alone and 13 to BioGlue repair. The animals were followed for morbidity and mortality, with a planned sacrifice at 90 days.

The results of this study revealed repair of aortic dissection using BioGlue as an adjunct to surgery in the sheep model was superior to surgery alone because:

- BioGlue decreased the incidence of acute post-repair rupture of the aorta from 30% to 0%.
- BioGlue decreased the incidence of re-dissection at the site of distal surgical repair from 17% to 0% in animals surviving 90 days.
- BioGlue decreased the incidence of dissection progression prior to healing from 17% to 0% in animal surviving 90 days.
- BioGlue decreased chronic dissection formation from 75% to 0% in animals surviving 90 days.

[1] Eddy CA, Choo S, McNally B, Elkins R. Creation and Repair of Acute Descending Aortic Dissection in Sheep. Abstract submitted to Aortic Surgery Symposium VI. 1998.

8.2.2 Thoracic Aorta Repair with BioGlue in Coagulopathic Sheep

The objective of this study was to investigate the efficacy of BioGlue as an anastomotic sealant of large diameter synthetic grafts. A coagulopathy was induced in sheep to enhance needle hole and surgical bleeding from synthetic grafts. Nine animals were treated with BioGlue and five control animals were treated with Surgicel® to effect hemostasis intra-operatively. Post-operative bleeding was measured throughout the perioperative period by chest tube output.

Post-surgical bleeding was significantly less in the BioGlue group compared to controls. Median total chest tube output decreased from 995 ml in the controls to 470 ml in the BioGlue group ($p<0.003$). Average hourly rate of blood loss was less in BioGlue group – 92.5 cc/hr as compared to the control group – 210 cc/hr ($p=0.005$).

8.2.3 Sutureless Coronary Artery Bypass Anastomoses: *In Vivo* and *In Vitro* Results

The objective of this study was to investigate the use of BioGlue with minimally invasive techniques for coronary artery bypass tissue-to-tissue anastomoses, using both *in vitro* and *in vivo* study methods.[2]

In Vitro Experiments

Anastomoses were made between cryopreserved human saphenous vein segments and coronary arteries *in vitro* on 12 intact bovine heart using BioGlue as the primary means of joining and sealing the vessels. (This was done to assess the feasibility of a glued anastomosis to facilitate attaching coronary artery bypass grafts during beating heart bypass procedures. There has been no human clinical use of the BioGlue in this application.) A total of 42 anastomoses were evaluated for anastomotic burst strength.

All grafts held a pressure of 300 mm Hg; 10 grafts were tested up to 560 mm Hg without leaks. All anastomoses were patent with no intraluminal BioGlue detected.

In Vivo Experiments

Three *in vivo* anastomoses of the left internal thoracic artery to the left anterior descending artery were constructed in goats, with evaluations at 24 hours, 10 months, and 1 year.

[2] Gundry SR, Black KS, and Izutani H. Sutureless coronary artery bypass with biologic glued anastomoses: Preliminary *in vivo* and *in vitro* results. J Thorac Cardiovasc Surg 2000; 120:473-7.

All anastomoses were patent, non-stenotic, and free of intraluminal BioGlue at all time points.

8.2.4 Experimental Technique of Aorto-Prosthetic Anastomoses

The objective of this study was to evaluate the short-term use of BioGlue with minimally invasive techniques on a tissue-to-synthetic graft (ePTFE) anastomosis in a growing pig.[3] Five pigs received a 6 mm inter-positional aortic ePTFE graft. The proximal anastomoses were repaired using BioGlue and the distal anastomoses were repaired using standard surgical suturing (7.0 polypropylene). The graft anastomoses were evaluated by duplex scan angiography, and histology at 1, 2, 3, 4, and 5 months.

All five pigs survived to the designated observation time. The graft patency was 80% (one graft thrombosed due to a technical error). The duplex scans demonstrated physiological proximal and distal aortic growth. No anastomotic leakage or dehiscence was observed at the BioGlue anastomosis in these animals that gained up to 60 kg during the study.

8.3 Biodegradation

Polymerized BioGlue is a protein cross-linked at its lysine side chains with glutaraldehyde. Cross-linked tissues remain sensitive to natural proteolysis, albeit at a substantially slower rate.

Polymerized BioGlue remained intact *in vitro* when kept in water over 30 days. Additionally, the histopathology of early (30 day) time points does not indicate dissolution of the implant.

When studied in various species and in varied implant sites, no implant degradation or resorption was observed for up to 12months. The sole observation of resorption was in a long-term (24 month) vascular BioGlue implant in sheep (see section 8.2.2). The 24-month sheep explant showed a range of phases of the remodeling of the BioGlue implant. Most regions exhibited minimal inflammatory activity (regions of encapsulation), while others showed signs of resorption. Cells infiltrated BioGlue as the resorption process evolved, laying down collagen as part of the normal healing process.

In humans, no chronic inflammatory response has been observed up to 9 months.

8.4 Immunotoxicity

[3] Glock Y, Roux D, Leobon B, Han SD, Delisle MB, Elias A, Fournial G. Experimental technique of aorto-prosthetic anastomoses by gluing (BioGlue® CryoLife). Presented at the Laparacopic Aortoiliac Surgery for Occlusive Disease and Aneruysms in Marseilles, France. January 28, 2000.

Table 2 summarizes the pre-clinical studies conducted for immunotoxicity assessment as they are listed in the FDA May 6, 1999 Immunotoxicity Guidance.

Table 2 – Immunotoxicity Guidance Study Compliance

Immunotoxic Effect	Immune Responses	Study	Results
Hypersensitivity	Humoral Response	Complement Activation	Pass
	Cellular/T-Cell Response	Buehler Hypersensitivity	Pass
		Kligman Hypersensitivity	Pass
	Humoral Response	Antigenicity Test of BioGlue in Guinea Pigs[2]	Skin results pass, low titers of IgG antibodies formed against BSA and BioGlue
		Intracutaneous Test in Rabbits	Pass
Inflammation	Histopathology (Cellular/Macrophage T-cell/Granulocyte Response) Host Resistance, Signs of Illness	90 day subcutaneous implant	Pass
		Aortic dissection study in sheep	Pass
		Coagulopathic sheep model study	Pass
Immunosuppression	Host Resistance Humoral	Complement Activation	Pass
	Host Resistance	90 day subcutaneous implant	Pass
		Aortic dissection study in sheep	Pass
		Coagulopathic sheep model study	pass
Immunostimulation	Histopathologic Signs of Illness	Complement Activation	Pass
		90 day subcutaneous implant	Pass
	Humoral response	Antigenicity test of BioGlue in guinea pigs	Pass, low titers of IgG antibodies formed against BSA and BioGlue
	Clinical Signs of Illness	90 day subcutaneous implant	Pass
Autoimmunity	Histopathology (Kidney, thyroid)[1]	90 day subcutaneous implant	Pass

1 Topical exposure of BioGlue extract. The Buehler test does not use adjuvant. The Kligman test uses adjuvant. The passing results from these two hypersensitivity tests showed a severity of 0, which by definition, is categorized as a Grade I weak allergenic potential response.

2 Subcutaneous exposure. This study had two parts; an active systemic anaphylaxis test and an antigen/antibody test. For the anaphylaxis test, guinea pigs received a subcutaneous application of either BioGlue or BSA as a sensitizing dose. After 14 days, the animals were then challenged with an additional dose of intravenously administered, adjuvant-added extract of BioGlue or BSA. A saline control was also administered. The animals showed a significant anaphylactic reaction to BSA, but on average, less than a weak reaction to BioGlue. Per ISO standards, a weak reaction is defined as a Grade I passing response. The second part of this experiment looked at the antigen/antibody potential after exposure to BioGlue or BSA. Eleven days after sensitization, diluted sera from the guinea pigs were tested against BioGlue, BSA, and a vehicle control antigen using ELISA techniques. Animals that received either BioGlue or BSA had low levels of antibody against BioGlue. However, the sensitized BioGlue animals had higher titers of antibody against BSA.

Based on hypersensitivity tests, there is a low risk of analphylactic reaction by the repeated use or long-term exposure to BioGlue. However, once sensitized, other medical devices or medicines containing bovine serum albumin theoretically may induce an anaphylactic reaction.

9. Summary of 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. A total of 175

patients were enrolled in this study. This included 54 non-randomized (lead-in) patients, 60 patients randomized to standard surgery plus BioGlue, and 61 patients randomized to standard surgery only. An interim analysis was performed after the 100th patient was enrolled into the randomized portion of the trial and had completed the 30-day follow-up period. There was no statistically significant difference in early mortality (primary endpoint) between the two groups; however, BioGlue-treated patients required fewer pledgets, hemostatic agents, and make-up stitches than the patients in the control group. There were no confirmed unanticipated adverse events, and no differences in adverse events between the two groups.

Based on data form the lead-in patients, CryoLife filed a Humanitarian Device Exemption (HDE) for the use of BioGlue as an adjunct in the surgical repair of acute thoracic aortic dissections, which was approved by FDA in December 1999 (H990007). CryoLife gained approval in May 2000 to investigate the use of BioGlue as an adjunct for sealing anastomotic sites in cardiac and vascular repairs, which is the subject of this PMA.

The following information is from the cardiac and vascular repair investigation:

9.1 Study Design

The BioGlue Effectiveness and Safety Trial as a Surgical Adjunct in Cardiac and Vascular Surgical Repairs was a prospective, multi-center, randomized, controlled trial. Patients were randomized to receive standard surgical repair with BioGlue applied to the anastomotic site prior to clamp removal (BioGlue group), or standard surgical anastomotic repair alone (control group). One patient crossed over from the control group to the BioGlue group due to uncontrolled bleeding. Data from this patient are included in the safety table, by omitted from the effectiveness table below. The overall objective was to collect clinical data concerning the safety and effectiveness of BioGlue used as an anastomotic sealant to provide hemostasis. The hypothesis was that hemostasis would be achieved in a higher percentage (delta 10%) of the BioGlue treated patient than in the control patients.

9.2 Patient Assessment

Safety and Effectiveness Evaluations

The BioGlue group and control group were compared to evaluate the following endpoints:

Primary Evaluation

- Anastomotic hemostasis (yes or no) of each of the repaired sites
  Anastomotic hemostasis was defined as an anastomosis that did 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.
- Anastomotic hemostasis (yes or no) on a per-patient basis

Patients with hemostasis 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

Safety Evaluation

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

9.3 Demographic Data

A total of 151 patients (76 in the BioGlue group, and 75 in the control group) were treated at 6 investigational sites in the cardiac and vascular repair arm of the U.S. IDE clinical trial. The patients were similar with respect to demographics (age, gender, race) distribution. Inclusion and exclusion criteria were chosen to minimize gender bias. The preponderance of male patients reflected both the gender referral pattern for cardiac disease and the severity of the disease in the centers involved. No important differences in success rate or adverse event rate were detected between males and females in this patient population, so the results presented are representative of both genders. Surgical procedures performed are shown in Table 3.

Table 3 – Cardiac and Vascular Procedures (All Randomized)

	Treatment Group			
System	**BioGlue Group**	**Control Group**	**Crossover**	**Total**
Cardiac Procedures[1]	24	25	0	49
Aortic Procedures[2]	57	47	1	105
Peripheral Vascular Procedures[3]	25	23	0	48
total	106	95	1	202

1 *Cardiac repairs included: aortic root replacement (4), aortoplasty (1), aortic valve annuloplasty (5), aortic valve re-suspension (1), aortic valve replacement (23), Bentall procedure (2), composite valved conduit procedure (8), mitral valve replacement (2), Ross procedure (2), coronary artery bypass grafting (1).*

2 *Aortic aneurysm repairs included: 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).*

3 *Peripheral vascular repairs included: 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).*

9.4 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 4 – Effectiveness Endpoints

Parameter of Interest	BioGlue Group (n = 76)	Control Group (n = 74)	Comments/ p value
Hemostasis success per patient[1]	61%	39%	0.014
Hemostasis success per anastomosis[2]	81%	57%	<0.003
RBC used 0 units 1-5 units >5 units	2.3 ± 3.6 37 29 10	1.9 ± 2.4 33 34 7	NS[4]
Platelets used 0 units 1-10 units >10 units	5.1 ± 10.1 47 21 8	5.2 ± 10.0 42 27 5	NS
Fresh Frozen Plasma used 0 units 1-10 units >10 units	3.8 ± 6.6 43 24 8	3.3 ± 5.0 41 23 9	NS
Cryoprecipitate used 0 units 1-10 units >10 units	4.3 ± 11.9 63 3 9	2.0 ± 8.3 67 1 4	NS
Donor Exposures 0 donors 1-20 donors >20 donors	 26 11 11	 23 15 13	NS
Pledgets used on primary repair	26% (53/202)	36% (66/184)	0.047
Make up stitches used	82% (31/38)[3]	81% (64/79)[3]	1.00
Hemostatic agent used	8% (3/38)[3]	10% (8/79)[3]	1.00
Additional BioGlue used	55% (21/38[3]	N/A	N/A
Other	8% (3/38)[3]	19% (15/79)[3]	0.17
Re-operation for bleeding	0	1 (1.4%)	One-sided 95% CI --, 0.9
Bypass time (min)	168.1 ± 67.6 (54 – 358), n=34	144.2 ± 60.6 (54-387), n=35	NS
Cross-clamp time (min)	74.0 ± 46.1 (10-196), n=54	69.1 ± 41.3 (19-196), n=55	NS
Total operative time (min)	237.7 ± 125.1 (85-650), n=75	228.7 ± 100.8 (60-515), n=73	NS
ICU time (days)	3.9 ± 5.6 (0-32), n=70	4.8 ± 7.1 (0-36), n=72	NS
Hospitalization time (days)	9.5 ± 10.6 (1-81), n=72	10.9 ± 9.7 (1-55), n=73	NS

1 Defined as hemostasis of 100% of the anastomotic repair sites
2 The average number of sites (anastomoses) per patient were 2.6 (range 1 to 8)
3 Denominator reflects number of patients in whom immediate hemostasis was not achieved
4 Not statistically significant

Safety Data

Table 5 – Safety Endpoints

Adverse Event Description	BioGlue Group N = 77			Control Group N = 74			*p* value
	n	%	#events	n	%	#events	
Pleural Effusion	20	26.0%	25	21	28.4%	22	0.855
Respiratory Dysfunction/Failure	13	16.9%	18	12	16.2%	15	1.000
Infection	13	16.9%	15	10	13.5%	13	0.653
Renal Dysfunction/Failure	13	16.9%	13	9	12.2%	10	0.492
Neurological Deficits	5	6.5%	6	16	21.6%	18	0.009
Death	5	6.5%	5	5	6.8%	5	0.999
Early (<30 days)	3	3.9%	3	2	2.7%	2	
3 month	1	1.3%	1	3	4.1%	3	
Hemorrhage	3	3.9%	3	3	4.1%	3	1.000
Ischemia	3	3.9%	3	2	2.7%	2	1.000
Organ System Dysfunction/Failure	3	3.9%	4	2	2.7%	2	1.000
Myocardial Infarction	3	3.9%	3	1	1.4%	1	0.620
Inflammatory, Immune Systemic Allergic Reaction[2]	2	2.6%	2	0	0%	0	0.497
Stroke or Cerebral Infarction	1	1.3%	1	3	4.1%	5	0.360
Paraplegia	1	1.3%	3	2	2.7%	3	0.615
Thromboembolism	1	1.3%	1	1	1.4%	4	1.000
Application of Adhesive to Non-Targeted Tissue[1]	1	1.3%	1	0	0%	0	1.000
Failure of Products to Adhere to Tissue[1]	1	1.3%	1	0	0%	0	1.000
Irreversible Morbidity	0	0%	0	1	1.4%	1	0.490
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, see Warnings and Precautions Sections of Instructions for Use*

2 *These adverse events were not device related. One patient had an allergic reaction to a preoperative antibiotic and the other patient had an allergic reaction to protamine sulfate.*

3 *Other adverse events observed in the BioGlue group were as follows: acidosis (1%), acute shortness of breath (1%), altered mental status (3%), anemia (5%), atelectasis (8%), cardiac arrythmia (22%), cerebral hemorrhage (1%), colecystitis (1%), coagulopathy (1%), congestive heart failure (4%), decreased femoral pulse (1%), deep vein thrombosis (1%), depression (4%), diarrhea (3%), sysphagia (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%), perforated viscus (1%), pericardial effusion (1%), urinary retention (4%), vocal cord paralysis (3%).*

4 *Other adverse events observed in the control group 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 arrythmia (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 group. There were no unanticipated adverse device effects (UADE) in this investigation.

Conclusion

The BioGlue group 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 anastomosis" 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 adverse events between BioGlue and control patients.

9.5 Device Failures and Replacements

No device failures or replacements occurred in the cardiac and vascular arm of the IDE clinical trial.

10 Conclusions Drawn from the Studies

10.1 Risk/Benefit Analysis

The absence of any significant adverse event related to the use of BioGlue, and the effectiveness of BioGlue in achieving anastomotic hemostasis and tissue reinforcement in cardiac and vascular repair, suggest that there is an acceptable risk/benefit ratio of the adjunctive use of BioGlue in cardiac and vascular repair.

10.2 Safety

The BioGlue implant and accessories demonstrated acceptable biocompatibility in *in vitro* and *in vivo* studies. In the U.S. IDE clinical trial, the absence of any significant adverse events related to BioGlue and similar rates of adverse events for the BioGlue group and standard surgical repair group support the safety of BioGlue in cardiac and vascular repair.

10.3 Effectiveness

The results of the preclinical and clinical testing have demonstrated a reasonable assurance of safety and effectiveness for BioGlue for its stated indication for use. A multi-center, randomized, controlled trial compared cardiac and vascular repair patients treated adjunctively with BioGlue prior to clamp removal to a standard surgical repair control group. BioGlue was noted to have a statistically higher rate of intra-operative anastomotic hemostasis when compared to the control group on both a "per patient" and a "per anastomosis site" basis. BioGlue-treated patients demonstrated a lower incidence of adjunctive pledget use on their primary repairs to achieve hemostasis.

11 Panel Recommendations

The Circulatory System Devices Panel met on September 11, 2001, and recommended approval of the BioGlue Surgical Adhesive. The Panel indicated that there were

inadequate data in the submission to support a claim that the blood management protocols used in hospitals will probably change, and thus recommended that such claims not be made. In addition, it was recommended that the sponsor re-analyze the p-value for the hemostasis endpoint to determine if there is a correlation of anastomosis sites within patients.

12 CDRH Decision

CDRH agreed with the recommendations of the Panel, and recommended approval after a re-analysis of the p-value for hemostasis, and additional cautionary statements were added to the labeling. Approval was granted on _____.

13 Approval Specifications

Directions for Use: See the labeling

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.