

# TRIDYNE™

## Vascular Sealant

The TRIDYNE™ Vascular Sealant package is provided sterile.

Information for the use of TRIDYNE™ Vascular Sealant is provided in this labeling for Physicians. **Before using TRIDYNE™ Vascular Sealant, please read the following information thoroughly.**

### 1.0 DEVICE DESCRIPTION

TRIDYNE™ Vascular Sealant (TRIDYNE™ VS) is a single-use medical device that is formed by mixing two components: (1) a solution of Human Serum Albumin (HSA) and (2) a synthetic crosslinking component of polyethylene glycol (PEG). Upon mixing, a clear, flexible hydrogel is formed.

TRIDYNE™ VS is supplied as a sterile, single-use, 2 - component kit which, when mixed makes a 4 mL total sealant volume for use in aortic surgery when adjunctive measures to achieve hemostasis are required by mechanically sealing areas of leakage. As TRIDYNE™ VS degrades it is metabolized and cleared primarily through the kidneys. Each kit includes:

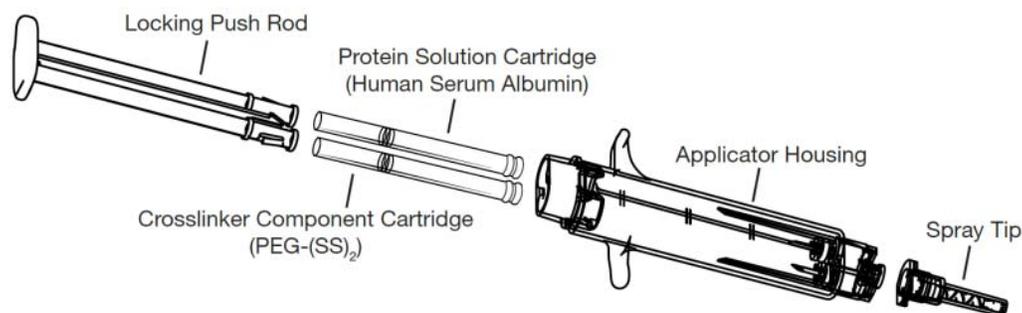
- One (1) - Chemistry Kit
  - One (1) preloaded cartridge containing 2 mL of Human Serum Albumin (HSA)
  - One (1) preloaded cartridge containing polyethylene glycol (PEG) as a dry white powder
- One (1) - Applicator Kit
  - One (1) 3 mL plastic syringe with needle
  - One (1) 5 mL vial of USP sterile water for injection (2 mL to be used to reconstitute PEG powder)
  - One (1) Applicator assembly with locking push rod
  - Two (2) Spray tips
- One (1) – Instructions for Use (Labeling)

Optional replacement spray tips are available as needed for convenience and positioning according to surgeon preference:

TRIDYNE™ VS Standard Spray Tips (pack of 2) Catalog # TDST0020, 10 units/box with Instructions

TRIDYNE™ VS Extended Spray Tip 6 in Catalog # TDET0006, 4 units/box with Instructions

**FIGURE 1 TRIDYNE™ Vascular Sealant Delivery System  
(Sterile Water and Syringe Not Shown)**



## **2.0 INTENDED USE / INDICATIONS FOR USE**

TRIDYNE™ Vascular Sealant is indicated for use in aortic surgery when adjunctive measures to achieve hemostasis are required by mechanically sealing areas of leakage.

## **3.0 DOSAGE, FORMS & STRENGTHS**

TRIDYNE™ VS is supplied as a 4 mL (total volume) kit.

## **4.0 CONTRAINDICATIONS**

- TRIDYNE™ VS is not for intravascular use.
- Do not use TRIDYNE™ VS in patients who have a history of allergic reaction to Human Serum Albumin, PolyEthylene Glycol or other device components.
- Do not apply TRIDYNE™ VS on oxidized regenerated cellulose, absorbable gelatin sponges or any other surface or material other than the target tissue or graft as adherence and intended outcome may be compromised.
- Do not use TRIDYNE™ VS in patients who have insufficient renal capacity for clearance of the polyethylene glycol load.

## **5.0 WARNINGS**

- Do not use TRIDYNE™ VS as a substitute for standard closure techniques.
- Excessive pressure against the vessel/graft edges or surrounding tissue during application may result in separation of the vessel/graft edges, allowing sealant into the vessel.
- Do not apply TRIDYNE™ VS when the vessel lumen is under negative pressure to avoid product from being drawn into the vessel (e.g., avoid applying in vessels that are not pressurized).
- Do not use more than 30 mL of TRIDYNE™ VS per patient.

- Do not allow non-polymerized TRIDYNE™ VS to contact circulating blood.

## 6.0 PRECAUTIONS

- The safety and effectiveness of TRIDYNE™ VS has not been established in the following:
  - Patients less than 18 years of age, pregnant or nursing women.
  - The presence of an active infection.
  - The presence of other sealants, hemostatic devices or products other than sutures and grafts. Patients receiving TRIDYNE™ VS in more than one application session (surgery) before and/or after resorption of TRIDYNE™ VS that was applied in any previous surgical session.
  - When mixed with any additive (e.g. antibiotics).
  - Coronary artery bypass grafts (CABG) or cardiac structures.
  - Operations other than aortic surgery with cardiopulmonary bypass.
- The use of ePTFE grafts or any vascular patches were not studied in the clinical trial.
- Do not use if sterile package or seal are damaged or open, as sterility may be compromised. Do not re-sterilize the contents.
- TRIDYNE™ VS should be refrigerated between 2°C and 8°C (36°F to 46°F). Do not freeze. Failure to do so may result in poor product performance.
- Do not use TRIDYNE™ VS after the expiration date, as sterility or performance may be compromised.
- Do not use reconstituted PEG solution after 20 minutes, as the performance of TRIDYNE™ VS may be compromised.
- Initial application in a wet field can lead to product dilution and affect product performance.
- Interruption of TRIDYNE™ VS application for approximately 10 seconds can result in clogging of the spray tip. If clogging occurs, remove the spray tip, wipe the end of the applicator to remove any fluid, and attach a new spray tip (provided) onto the end of the applicator.
- TRIDYNE™ VS is intended for single use only. Do not reuse any component.
- Human Serum Albumin – HSA (USP) in the TRIDYNE™ VS kit is obtained from an FDA licensed supplier and the protein is derived from plasma collected from donors who have been screened and tested according to the methods specified by the FDA. These methods minimize the possibility that drawn blood will contain communicable diseases or viruses such as hepatitis and HIV.
- Do not apply TRIDYNE™ VS to anastomoses or vascular suture lines when the vessel lumen is under suction or negative pressure to avoid unpolymerized product being drawn into the vessel as this may result in local thrombus or distant vascular embolism.
- Do not use blood saving devices when suctioning excess sealant from the surgical field.
- TRIDYNE™ VS resorption time in humans has not been studied. In rats, over 50% of a 14C-labeled device was excreted after 24 hours and virtually all radioactivity was recovered from rats at 14 days post-implant. TRIDYNE™ VS was largely absent at 4 days with only isolated fragments of TRIDYNE™ VS apparent at 7 days after implementation on porcine tissue.

- Discard unused material in accordance to standard practice for TRIDYNE™ VS components.
- The sealant may swell up to a maximum of 17.3% in any dimension or 61.5% in volume. Caution should be taken when applying sealant to confined areas where sealant swelling could impinge on adjacent structures.

## **7.0 ORIGINAL PIVOTAL CLINICAL STUDY**

Study Title: A Prospective, Randomized Study to Compare TRIDYNE™ Vascular Sealant to GELFOAM® PLUS as an Adjunct for the Control of Bleeding in Subjects Undergoing Thoracic Aortic Surgery.

### **7.1 Study Objectives**

The primary study objective was to compare the time to hemostasis at the aortic anastomotic suture lines involving the aortic valve, ascending aorta, or aortic arch while on cardiopulmonary bypass in subjects randomized to TRIDYNE™ VS compared to subjects randomized to Control (GELFOAM® PLUS).

### **7.2 Study Design**

This was a prospective, multicenter, randomized, single-blind (subject), superiority trial to evaluate the safety and effectiveness of the TRIDYNE™ VS compared to Control for the control and prevention of intraoperative bleeding after conventional reconstructions during thoracic surgery on the aorta. Subjects were randomized 2:1 to TRIDYNE™ VS or Control respectively. The Control was GELFOAM® PLUS, supplied as a ready to use medical device kit containing GELFOAM® Sterile Sponge, Thrombin (Human) lyophilized powder, two 10 mL Prefilled Saline Syringes (0.9% Sodium Chloride Injection USP), and a Vial Access Device. The GELFOAM® Sterile Sponge component is an absorbable gelatin sponge (USP) measuring 100 cm<sup>2</sup> (8 x 12.5 cm).

Subjects scheduled for non-emergent, thoracic surgery involving the aortic valve, ascending aorta, or aortic arch on cardiopulmonary bypass with or without concomitant coronary artery bypass graft (CABG) procedure(s) were assessed for eligibility.

### **Key Eligibility Criteria**

#### Preoperative Inclusion Criteria:

1. Subject must be  $\geq 18$  years of age.
2. Subject is scheduled for elective, primary thoracic surgery involving the aortic valve, ascending aorta, or aortic arch on cardiopulmonary bypass.
3. Subject has an expected life expectancy  $\geq 6$  months.
4. Subject is willing and able to comply with all aspects of the study including follow-up schedule.
5. Subject or authorized representative, has the ability to provide voluntary written informed consent.

Intraoperative Inclusion Criteria:

6. Subject is able to undergo an antegrade cardioplegia injection for evaluation of a leak at the aortic anastomotic site(s) during the procedure.
7. Following this injection, subject has a leaking site where a topical sealant/hemostatic agent may be used to control bleeding.

**Exclusion Criteria**

1. Subject has Type A or other acute thoracic aortic dissection.
2. Subject has undergone prior thoracic surgery (open thoracotomy not including interventional cardiology procedures).
3. Subject is undergoing a planned concomitant procedure other than coronary artery bypass graft (CABG).
4. Subject has a previous organ transplant.
5. Subject has known or suspected preoperative coagulation disorder.
6. Subject is allergic to human thrombin or has a history of allergic reactions after application of human thrombin.
7. Subject is allergic to protamine.
8. Subject has a Left Ventricular Assist Device (LVAD) or planned to receive an LVAD.
9. Subject is undergoing emergency surgery.
10. Subject is in chronic renal failure.
11. Subject has a hematocrit < 21% pre-operatively.
12. Subject has a serum creatinine  $\geq 2.5$  mg/dl at baseline or is currently on dialysis.
13. Subject has a cardiac ejection fraction < 25%.
14. Subject is scheduled for another cardiac surgery within 30 days of enrollment.
15. Subject has an active or latent infection which is systemic or at the intended surgery site.
16. Subject is immuno-compromised such as that resulting from chronic oral steroid use, chemotherapeutic agents, or immune deficiency disorders.
17. Subject is pregnant by a positive pregnancy test or has plans to become pregnant during the study period or is currently breast-feeding.
18. Subject is unwilling to receive blood products.
19. Subject has participated in another investigational research study within 30 days of enrollment.
20. In the opinion of the Investigator, the subject has a clinical condition that would preclude the use of the study device, preclude the subject from completing the follow-up requirements, or would complicate the evaluation of this study.

Subjects with at least one confirmed leaking site after final antegrade cardioplegia injection were randomized to either TRIDYNE™ VS or Control. Time to hemostasis (TTH) measurement began after either TRIDYNE™ VS or Control was applied to the anastomotic suture line(s) and bypass cross clamp was released. Hemostasis was assessed continuously until hemostasis was achieved at each applied anastomotic site or up to 10 minutes.

Immediate hemostasis was defined as zero (0) seconds or no observable bleeding from the time the clamps were released to achieving hemostasis.

Additional standard of care surgical hemostatic measures could be performed (e.g. other sealants, stitches, pledgets, administration of protamine, manual pressure) if hemostasis was not achieved at the anastomotic suture line after 10 minutes or it was deemed by the surgeon to be medically necessary.

Post operatively, subjects were monitored to assess hemostasis, chest tube output, transfusion volumes and safety. Subjects were followed for 30 days post index procedure.

Safety data were reviewed by a Clinical Events Committee (CEC).

### **7.3 Clinical Endpoints**

The primary effectiveness endpoint of this study was the time to achieve hemostasis at the aortic anastomotic suture line from the time surgical clamps were released to cessation of leakage at the treated anastomotic site with either TRIDYNE™ VS or Control.

Safety endpoints included adverse events and device-related adverse events from the time of randomization through the end of study participation, study completion or 30 days post-operatively.

This study also assessed the following secondary endpoints:

1. Proportion of subjects who achieved successful hemostasis at all treated aortic anastomotic suture lines following assigned treatment. Success was defined as hemostasis obtained within 5 minutes.
2. Proportion of subjects who achieved immediate hemostasis, defined as 0 seconds, at all treated aortic anastomotic suture lines following assigned treatment.
3. Chest tube drainage volume within 24 hours following surgery.
4. Total transfusion volume within 24 hours following surgery.
5. Time between cross clamp removal and request of surgical wires for sternal closure.
6. Incidence of reoperations for aortic bleeding complications following assigned treatment through 30 days.
7. Number of device-related serious adverse events per patient following assigned treatment through 30 days.

### **7.4 Subject Accountability**

A total of 204 subjects were consented and enrolled into the study of which 158 were randomized. Of the 158 randomized subjects (107 TRIDYNE™ VS and 51 Control), 153 subjects completed the study. Disposition of the 5 subjects that did not complete the study: 2 subjects were randomized and not treated, 3 subjects prematurely discontinued due to death; 2 (1.9%) from the TRIDYNE™ VS treatment group and 1 (2.0%) from the Control group.

Table 1 provides a summary of the subject accountability.

**Table 1 Subject Accountability**

	<b>TRIDYNE™ VS n (%)</b>	<b>Control n (%)</b>	<b>Total n (%)</b>
Enrolled			204
Not randomized			46
Eligibility Criteria Not Met <sup>1</sup>			38
Sponsor's Decision <sup>2</sup>			5
Withdrawal of Consent			3
Randomized (Intent to Treat)	107 (100.0)	51 (100.0)	158 (100.0)
Treated (Modified Intent to Treat) <sup>3</sup>	106 (99.1)	50 (98.0)	156 (98.7)
Randomized Not Treated <sup>4</sup>	1 (0.9)	1 (2.0)	2 (1.3)
Discharged after Index Procedure	107 (100.0)	50 (98.0)	157 (99.4)
Completed one month follow-up	104 (97.2)	49 (96.1)	153 (96.8)
Primary reason for discontinuation			
Death	2 <sup>5</sup> (1.9)	1 <sup>6,7</sup> (2.0)	3 (1.9)

1. Preoperative Inclusion not met: One Subject was not scheduled for elective, primary thoracic surgery involving the aortic valve, ascending aorta, or aortic arch on cardiopulmonary bypass. Intraoperative Inclusion Criteria not met: Two subjects were unable to undergo an antegrade cardioplegia injection for evaluation of a leak at the aortic anastomotic site(s) during the procedure. Twenty subjects did not have a leaking site where a topical sealant/hemostatic agent may be used to control bleeding following cardioplegia injection. Exclusion Criteria: One subject had thoracic surgery (open thoracotomy not including interventional cardiology procedures). Eight subjects had a planned concomitant procedure other than coronary artery bypass graft (CABG). One subject had a previous organ transplant. Two subjects had a known or suspected preoperative coagulation disorder. One subject had a serum creatinine greater than or equal to 2.5 mg/dl at baseline. Three subjects had an active or latent infection which is systemic or at the intended surgery site. One subject was immunocompromised such as that resulting from chronic oral steroid use, chemotherapeutic agents, or immune deficiency disorders. One subject had participated in another investigational research study within 30 days of enrollment. Three subjects in opinion of investigator had a clinical condition that would preclude use of study device, preclude subject from completing follow-up requirements, or complicate evaluation of study.
2. Subjects met eligibility criteria but were not randomized as enrollment numbers were already met.
3. The subjects that were treated represent the modified intent to treat population.
4. Two Control subjects and one TRIDYNE™ VS subject were randomized, however, the cross clamp was removed prior to application of the sealant.
5. Subject deaths due to cardiac arrest and ischemic cardiomyopathy.
6. Subject died during hospitalization and therefore was not discharged.
7. Subject death due to gastrointestinal bleed.

All subsequent data presented is utilizing the Modified Intent-to-Treat population unless otherwise indicated.

## 7.5 Demographics

A total of 156 subjects were treated (2 subjects were randomized and not treated, 1 TRIDYNE™ VS and 1 Control) across 19 investigational sites.

Table 2 provides a summary of subject demographic characteristics.

**Table 2 Subject Demographic Characteristics**

		<b>TRIDYNE™ VS</b>	<b>Control</b>	<b>Total</b>
<b>Number of subjects treated</b>		<b>106</b>	<b>50</b>	<b>156</b>
Age (years)	Mean (SD)	61.5 (14.42)	62.4 (14.30)	61.8 (14.34)
	Median	63.5	64.0	64.0
	Min-Max	23.0 - 87.0	20.0 - 89.0	20.0 - 89.0
Age Categories (years)				
	< 65	54 (50.9%)	28 (56.0%)	82 (52.6%)
	≥ 65	52 (49.1%)	22 (44.0%)	74 (47.4%)
Gender	Male	74 (69.8%)	35 (70.0%)	109 (69.9%)
	Female	32 (30.2%)	15 (30.0%)	47 (30.1%)
BMI (kg/ m <sup>2</sup> )	Mean (SD)	31.2 (7.52)	28.3 (5.50)	30.2 (7.05)
	Median	30.1	27.5	29.2
	Min-Max	19.9 - 60.1	17.4 - 41.9	17.4 - 60.1
Ethnicity	Hispanic or Latino	2 (1.9%)	3 (6.0%)	5 (3.2%)
	Not Hispanic or Latino	100 (94.3%)	44 (88.0%)	144 (92.3%)
	Unknown	4 (3.8%)	3 (6.0%)	7 (4.5%)
Race				
	American Indian	2(1.9%)	0 (0.0%)	2 (1.3%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black or African American	3 (2.8%)	3 (6.0%)	6 (3.8%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (2.0%)	1 (0.6%)
	White Caucasian	94 (88.7%)	43 (86.0%)	137 (87.8%)
	Other	1 (0.9%)	0 (0.0%)	1(0.6%)
	Unknown	6 (5.7%)	3 (6.0%)	9 (5.8%)

## 7.6 Types of Surgical Procedures

There were 156 subjects treated overall with 172 treated suture lines; 119 suture lines in the TRIDYNE™ VS group and 53 treated suture lines in the Control group.

Table 3 provides the number of suture lines treated in the different types of surgeries.

**Table 3 Number of Suture Lines Treated in Various Surgery Types**

	<b>TRIDYNE™ VS n = 119</b>	<b>Control n = 53</b>	<b>Total n = 172</b>
Surgery type			
Aortic Aneurysm Repair	18 (15.1%)	7 (13.2%)	25 (14.5%)
Aortic Root Replacement	16 (13.4%)	8 (15.1%)	24 (14.0%)
Aortic Valve Procedure	50 (42.0%)	30 (56.6%)	80 (46.5%)
Ascending Aorta Replacement	28 (23.5%)	5 (9.4%)	33 (19.2%)
Other	7 <sup>1</sup> (5.9%)	3 <sup>2</sup> (5.7%)	10 (5.8%)

1. One subject had hemiarch. One subject had aortic root replacement and aortic aneurysm repair. Two subjects had aortic valve procedure and aortic aneurysm repair. Two subjects had aortic valve replacement, ascending aorta replacement and aortic root replacement. One subject had aortic root replacement and ascending aorta replacement.

2. One subject had aortic valve replacement and hemiarch procedure. One subject had aortic valve replacement. One subject had David procedure, aorta root replacement and ascending aorta replacement.

## 7.7 Number of Treatment Sites and Amount of Product Used per Subject

Some subjects had more than one suture line treated. The number of suture lines treated and the amount of product used per subject is presented below.

Table 4 provides the number of subjects that had more than one suture line treated.

**Table 4 Number of Treated Suture Lines by Treatment Group**

Treated Suture Lines	Treatment Group		Total n = 156
	TRIDYNE™ VS n = 106	Control n = 50	
1	93 (87.7%)	47 (94.0%)	140 (89.7%)
2	13 (12.3%)	3 (6.0%)	16 (10.3%)

Table 5 provides the amount of product that each subject received.

**Table 5 Amount of Product Used per Subject**

	TRIDYNE™ VS (mL) n = 106	Control (cm x cm) n = 49 <sup>1</sup>
Mean (SD)	3.3 (2.25)	117.9 (206.9)
Min-Max	0.5 - 12.0	2.0 - 864.0

1. Amount of product used was not recorded for one subject therefore the denominator is 49.

## 7.8 Safety and Effectiveness Results

### 7.8.1 Safety Results

Overall, there were no major differences in the incidence of adverse events between treatment groups.

#### Serious Adverse Events

Approximately half of the subjects in each treatment group experienced a SAE while in the study (51 subjects [48.1%] treated with TRIDYNE™ VS, 29 subjects [58.0%] treated with Control). Seven SAEs, described below, were considered by the Clinical Events Committee (CEC) to be possibly device-related (3 patients [2.8%] treated with TRIDYNE™ VS 4 patients [8.0%] treated with Control).

Nearly all CEC adjudicated SAEs were considered to be related to the procedure (87 of 88 SAEs in patients treated with TRIDYNE™ VS 48 of 48 SAEs in patients treated with the Control). Most SAEs occurred in only one or two patients in either treatment group, with the exception of atrial fibrillation that occurred in 27 patients (25.5%) treated with TRIDYNE™ VS and 17 patients (34.0%) treated with the Control. Some of these were considered not to be serious by the Investigator and were upgraded by the CEC as a result of treatment by cardioversion or prophylactic use of antiarrhythmics.

The CEC adjudicated seven patients SAEs to be possibly device-related following completed surgery through the follow-up evaluation; 3 (2.9%) in the TRIDYNE™ VS treatment group and 4 (8.2%) in the Control treatment group. None of the SAEs were unexpected given the procedures performed. The events are described below:

TRIDYNE™ VS SAEs

- Patient had a cerebrovascular accident on Study Day 1, which was severe in intensity.
- Patient had a cerebrovascular accident on Study Day 15, which was severe in intensity.
- Patient had pericardial effusion on Study Day 4, which was considered moderate in intensity. The subject underwent mediastinal re-exploration which found serosanguineous pericardial effusion with no active bleeding. Surgery was completed without complication and the event was considered resolved on Study Day 9.

Control SAEs

- Patient had a cerebrovascular accident on Study Day 1, which was moderate in intensity.
- Patient had a cerebrovascular accident on Study Day 0, which was moderate in intensity.
- Patient had a hematoma on Study Day 0, which was moderate in intensity. The patient was taken back to the operating room on the same day for mediastinal re-exploration where a large amount of hematoma in the mediastinum was noted and evacuated.
- Patient reported hypotension on Study Day 0, which was moderate in intensity.

Non-Serious Adverse Events

At least one non-serious AE was reported in almost all of the patients in this study (92.5% of patients treated with TRIDYNE™ VS and 100.0% of patients treated with Control).

Table 6 lists AEs occurring in 5% or more of either treated or Control patients. None of these were CEC adjudicated to be device-related.

**Table 6 Number of Patients with Frequently Reported (Greater than 5% in Either Treatment Group) Adverse Events**

<b>Adverse Event</b>	<b>TRIDYNE™ VS n = 106</b>	<b>Control n = 50</b>
Pleural effusion	43 (40.6%)	18 (36.0%)
Anemia	39 (36.8%)	13 (26.0%)
Atelectasis	37 (34.9%)	15 (30.0%)
Atrial fibrillation	27 (25.5%)	17 (34.0%)
Leukocytosis	25 (23.6%)	13 (26.0%)

<b>Adverse Event</b>	<b>TRIDYNE™ VS n = 106</b>	<b>Control n = 50</b>
Thrombocytopenia	19 (17.9%)	8 (16.0%)
Peripheral Edema	18 (17.0%)	4 (8.0%)
Nausea	16 (15.1%)	7 (14.0%)
Fluid overload	14 (13.2%)	9 (18.0%)
Hypotension	13 (12.3%)	5 (10.0%)
Pulmonary Edema	11 (10.4%)	2 (4.0%)
Pneumothorax	10 (9.4%)	5 (10.0%)
Hyperglycemia	9 (8.5%)	6 (12.0%)
Hypoxia	8 (7.5%)	3 (6.0%)
Hypokalemia	7 (6.6%)	2 (4.0%)
Back pain	7 (6.6%)	2 (4.0%)
Tachycardia	6 (5.7%)	2 (4.0%)
Dizziness	6 (5.7%)	3 (6.0%)
Renal injury	5 (4.7%)	3 (6.0%)
Dyspnea	4 (3.8%)	3 (6.0%)
Fatigue	3 (2.8%)	5 (10.0%)
Hyponatremia	3 (2.8%)	3 (6.0%)
Respiratory failure	3 (2.8%)	3 (6.0%)
Atrial flutter	2 (1.9%)	3 (6.0%)
Pyrexia	2 (1.9%)	3 (6.0%)
Musculoskeletal pain	2 (1.9%)	4 (8.0%)
Vomiting	1 (0.9%)	4 (8.0%)
Musculoskeletal chest pain	0 (0.0%)	3 (6.0%)

There were 2 patients, one in each treatment group, with reported AEs considered device-related by the Investigator. The subject treated with TRIDYNE™ VS reported azotemia on Study Day 10, which the Investigator considered to both related to the device and procedure. The event was mild in severity and was adjudicated by the CEC not related to the device. The subject treated with the Control reported nausea on Study Day 5, which the Investigator considered possibly related to the device and definitely related to the procedure. The event was mild in severity and was adjudicated by the CEC not related to the device.

#### Unanticipated Adverse Device related Events (UADE)

No adverse events were considered to be UADEs.

#### Patient Deaths

There were three patient deaths during the study; two deaths (cardiac arrest, ischemic cardiomyopathy) in the TRIDYNE™ VS group and one death (gastrointestinal bleed) in the Control group. None of the deaths were considered by the Investigators or adjudicated by the CEC to be device related.

## 7.8.2 Effectiveness Results

### Primary Effectiveness Endpoint

The primary endpoint was evaluated by the following hypothesis:

H<sub>0</sub>: The mean time to hemostasis for subjects receiving TRIDYNE™ VS at leaking sites involving the aortic valve, ascending aorta, or aortic arch is the same as for subjects receiving Control.

H<sub>1</sub>: The mean time to hemostasis for subjects receiving TRIDYNE™ VS at leaking sites involving the aortic valve, ascending aorta, or aortic arch is different for subjects receiving Control.

The distribution of time to hemostasis was significantly different between the TRIDYNE™ VS treatment group and Control treatment group (Wilcoxon rank-sum test p-value < 0.0001). The adjusted mean time to hemostasis was lower in subjects in the TRIDYNE™ VS treatment group compared to subjects in the GELFOAM® PLUS treatment group (124.3 seconds compared to 377.8 seconds). The term ‘adjusted’ is used because an imputation to a value of 600 seconds was used in subjects that did not achieve hemostasis in 10 minutes. This imputation technique underestimated the time to hemostasis for the subjects who did not achieve hemostasis by 600 seconds. Since more subjects in Control group did not achieve hemostasis by 600 seconds, this likely provided a conservative assessment of the TTH comparison.

Table 7 provides the adjusted mean and minimum-maximum time to hemostasis. The time to hemostasis is missing for one subject; therefore, the denominator is 105 subjects.

**Table 7 Time to Hemostasis (Seconds) for Individual Subjects**

<b>Treatment</b>	<b>n</b>	<b>Adjusted Mean</b>	<b>Adjusted Min-Max</b>
TRIDYNE™ VS	105	124.3	0.0 - 600.0
Control	50	377.8	0.0 - 600.0

If immediate hemostasis was achieved, 0 minutes was used as time to hemostasis (TTH). If hemostasis was not achieved within 10 minutes (600 seconds), 10 minutes (600 seconds) was used as the TTH. Imputation was performed for subjects who did not achieve hemostasis in 10 minutes (600 seconds). 10 minutes (600 seconds) was used as the TTH in this group. This imputation technique results in an underestimation of the TTH when hemostasis was not achieved in 10 minutes (600 seconds).

For subjects with more than one aortic anastomotic suture line treated, the site with longest TTH was used for analysis.

### Secondary Effectiveness Endpoint

Immediate hemostasis defined as hemostasis at 0 seconds was achieved in 60.0% of subjects treated with TRIDYNE™ VS compared to 16.0% of subjects treated with Control. The percentage of subjects that achieved hemostasis within 10 minutes for TRIDYNE™ VS was 87.6% compared to 52.0% for the Control. By the 10-minute cut-off, only 12.4% of subjects in the TRIDYNE™ VS treatment group failed to achieve hemostasis, compared to 48.0% of the subjects in the Control treatment group.

Table 8 provides the information regarding whether hemostasis was immediate, successful

(within 5 minutes), or within 10 minutes. The time to hemostasis is missing for one subject; therefore, the denominator is 105 subjects.

**Table 8 Summary of Time to Hemostasis for Individual Subjects**

	<b>TRIDYNE™ VS n = 105</b>	<b>Control n = 50</b>
Immediate (0 second)	63 (60.0%)	8 (16.0%)
0 < TTH < 5 minutes	90 (85.7%)	20 (40.0%)
0 < TTH <10 minutes	92 (87.6%)	26 (52.0%)

If the immediate hemostasis was achieved, 0 minutes was used as time to hemostasis (TTH). For subjects with more than one aortic anastomotic suture line treated, the site with longest TTH was used for analysis.

#### Use of Additional Adjunctive Agents to Achieve Hemostasis

As described above, additional standard of care surgical hemostatic measures could be performed if hemostasis was not achieved at the anastomotic suture line after 10 minutes or it was deemed by the surgeon to be medically necessary.

Table 9 describes the adjunctive treatments of the anastomotic suture lines. The denominator is the total number of suture lines treated.

**Table 9 Summary of Adjunctive Treatment of Aortic Anastomotic Suture Lines<sup>1</sup>**

	<b>TRIDYNE™ VS n = 119</b>	<b>Control n = 53</b>	<b>Total n = 172</b>
None	86 (72.3%)	17 (32.1%)	103 (59.9%)
Additional application(s) of assigned treatment	16 (13.4%)	13 (24.5%)	29 (16.9%)
Sutures	18 (15.1%)	14 (26.4%)	32 (18.6%)
Pledgets	2 (1.7%)	2 (3.8%)	4 (2.3%)
Protamine	3 (2.5%)	8 (15.1%)	11 (6.4%)
Manual Pressure	0 (0.0%)	3 (5.7%)	3 (1.7%)
Other <sup>2</sup>	4 (3.4%)	6 (11.3%)	10 (5.8%)

1. Data was analyzed by suture line, not per subject.

2. Other includes: BioGlue, Gelfoam, and Thrombin.

### **7.8.3 Other Secondary Endpoints Results**

- The amount of chest tube drainage within 24 hours of surgery was not significantly different between groups.
- There was no significant difference of total transfusion volume between the treatment groups.
- There was no appreciable difference in surgical time between subjects treated with TRIDYNE™ compared to subjects treated with Control.
- There was no appreciable difference in the time between cross clamp removal and request of surgical wires for sternal closure.

- One subject (Control treatment group) required a reoperation for aortic bleeding complications following completed surgery through 30 days.

## 8.0 POTENTIAL ADVERSE EVENTS

Table 10 lists the potential adverse events that have been associated with this class of surgical sealants.

**Table 10 Potential Adverse Events Associated with Surgical Sealants**

A hypersensitivity reaction such as swelling or edema at the application site
Thrombosis and thromboembolism
An exacerbation of renal dysfunction in patients with pre-existing or unknown renal disease
Failure of the sealant to adhere to target tissue
Failure of the sealant to stop diffuse persistent bleeding
Possible transmission of infectious agents from materials of human origin.
Application of the sealant to tissue not targeted for the procedure.

Table 11 lists the potential adverse events that have been associated with aortic procedures:

**Table 11 Potential Adverse Events Associated with Aortic Procedures**

Adhesions	Lymphocele / lymph fistula
Aneurysm and anastomotic pseudoaneurysm	Myocardial infarction
Aortic insufficiency	Neurological deficits
Cardiac tamponade	Organ system dysfunction / failure
Cerebral emboli	Pain
Coagulopathy	Paraplegia
Death or irreversible morbidity	Pleural effusion
Dissection	Pulmonary Emboli
Edema	Pyrexia
Emboli	Renal dysfunction / failure
Erythema	Stroke or cerebral infarction
Graft occlusion	Thrombosis
Hematoma	Vasospasm
Hemorrhage	Vessel dissection
Infection	Vessel occlusion
Injury to normal vessels or tissue	Vessel rupture and hemorrhage
Ischemia	

## 9.0 PATIENT COUNSELING INFORMATION

The physician should discuss the following with patients potentially receiving TRIDYNE™ VS:

- The indication for TRIDYNE™ VS use

- The risks and benefits associated with TRIDYNE™ VS use

## **10.0 DIRECTIONS FOR USE**

TRIDYNE™ Vascular Sealant is indicated for use in aortic surgery when adjunctive measures to achieve hemostasis are required by mechanically sealing areas of leakage.

### **Assess for Bleeding**

After standard closure of aortic incisions, assess for bleeding. If bleeding is observed, consider applying TRIDYNE™ VS.

If a patient is a candidate for TRIDYNE™ VS use, perform the following steps:

### **Inspect Packaging**

The TRIDYNE™ VS kit consists of two sealed, sterile packages. Contents:

- One (1) - Chemistry Kit, e-beam sterilized
  - One (1) preloaded cartridge containing 2 mL of HSA
  - One (1) preloaded cartridge containing PEG as a dry white powder
- One (1) - Applicator Kit, Ethylene Oxide sterilized
  - One (1) 3 mL plastic syringe with needle
  - One (1) 5 mL vial of USP sterile water for injection (used for reconstitution of the PEG powder)
  - One (1) Applicator assembly with locking push rod
  - Two (2) Spray tips
- One (1) – Instructions For Use insert (Labeling)

If package and/or product integrity have been compromised (i.e. damaged package seal, or broken components), do not use or re-sterilize the contents. Refer to Warnings and Precautions as listed in Sections 5 & 6 of this labeling.

### **Prepare TRIDYNE™ Vascular Sealant**

Using aseptic technique, open the sterile package and pass the contents into the sterile field.

### **Follow These Steps:**

#### **Step 1**

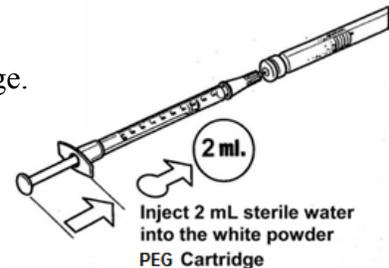
Draw 2 mL of sterile water into the syringe and express all air out of the syringe (syringe and sterile water are provided in the Applicator Kit).



## Step 2

Inject the 2 mL of sterile water into the cartridge containing the PEG.

NOTE: The HSA cartridge contains a yellow liquid. Water should only be injected into the PEG (white powder) cartridge.



## Step 3

Mix sterile water and the PEG in the cartridge by gently rocking the cartridge from end to end (generally 1-2 minutes) until the solution contains no undissolved powder. When all powder is dissolved, the PEG is ready for use.

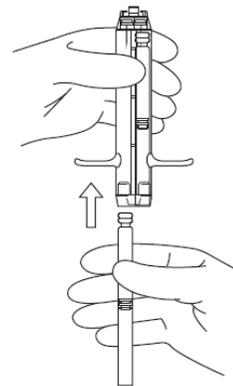
NOTE: TRIDYNE™ VS should be used within 20 minutes of dissolving the PEG in water.



## Step 4

Before the spray tip is attached, point the applicator tip up and load each cartridge into the twin-chambered applicator housing. Gently press the cartridges to seat them into place. Cartridges may be loaded into either chamber of the applicator housing.

NOTE: When properly loaded the chemistry cartridges should sit flush with the end of the applicator housing.

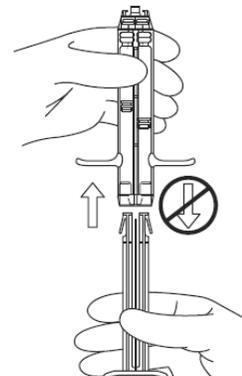


Load HSA and PEG Cartridges into Applicator Housing

### Step 5

Without the spray tip attached, point the applicator tip upward to allow any air in the chemistry cartridges to rise to the top of the cartridges. Insert the locking push rod into the openings in the rear of the cartridges until it snaps into place.

NOTE: During applicator assembly, the push rod is designed to lock into the applicator housing. Forced removal of the locking push rod from the applicator housing may result in potential damage to the applicator components or the chemistry cartridges.

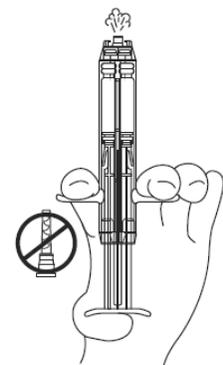


Insert the Locking Push Rod

### Step 6

With the tip of the applicator pointed upward, briskly flick the applicator to free any air bubbles. Express the air by pushing up on the push rod until the stoppers in each cartridge are aligned with one another. Wipe the applicator tip as often as needed with clean, sterile gauze to remove any liquid that may have been expressed with the air. Wipe the openings from front to back not side to side to avoid mixing of components.

Take care to express as little fluid as possible during this process.



Express air



### Step 7

Place a spray tip on the end of the applicator and rotate the spray tip clockwise  $\frac{1}{4}$  turn until locked.



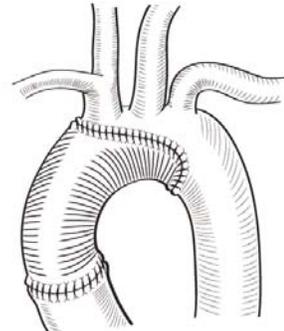
### Step 8

The TRIDYNE™ VS is ready for application.

### Step 9

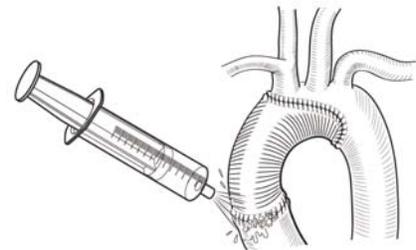
After standard closure of the suture lines during aortic surgery, assess for bleeding. If bleeding is observed, consider applying TRIDYNE™ VS. Select the target site to be sealed.

NOTE: Each 4 mL TRIDYNE™ VS Kit is intended to cover an area approximately  $40 \text{ cm}^2$  ( $6 \text{ in}^2$ ) and 1 mm thick.



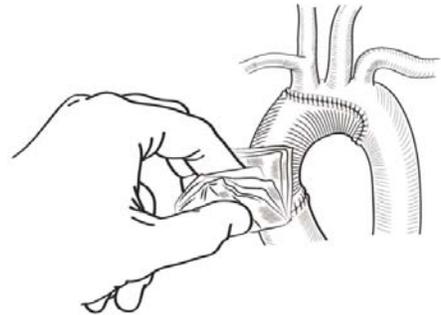
### Step 10

Rinse the surface intended to be treated with sterile saline to remove any pooled blood or blood clots with irrigation and/or suction.



### Step 11

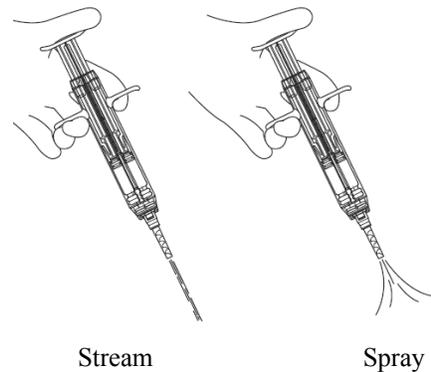
Blot the intended treatment area with a sponge or gauze to remove excess moisture.



### Apply TRIDYNE™ VS

### Step 12

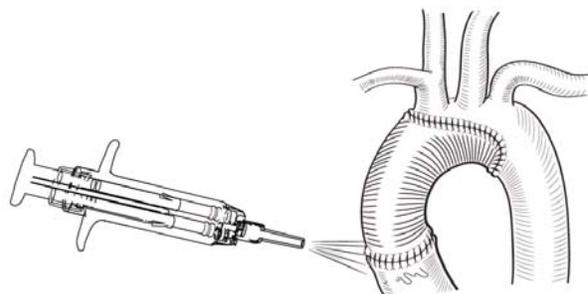
Position the applicator tip over the target area and apply pressure to the push rod to dispense the sealant. Gentle pressure on the push rod will yield a slow, targeted stream while firm, steady pressure will transition the stream to a spray.



### Step 13

Maintain pressure on the push rod to deliver desired spray or stream onto the target site.

NOTE: Do not apply TRIDYNE™ VS to anastomoses or suture lines when the vessel lumen is under negative pressure or suction (e.g. vessels that are not pressurized) to avoid unpolymerized product being drawn into the vessel as this may result in local thrombus or distant vascular embolism.



### Step 14

TRIDYNE™ VS will form a flexible hydrogel two minutes after application. Assess the site for hemostasis after two minutes. TRIDYNE™ VS application over a site that has continued bleeding may be repeated.

### Step 15

If the applicator's contents are not entirely used, immediately remove the spray tip and wipe residual TRIDYNE™ VS from the applicator tip with sterile dry gauze to prevent clogging.

### Step 16

If additional kits are required follow the product preparation instructions provided above.

NOTE: 7.5 kits (30 mL) is the maximum number of kits to be used on one patient.

### Step 17

 After use, TRIDYNE™ VS may be a potential biohazard. Handle and dispose of in accordance with any local and federal laws regarding medical waste. Discard unused material in accordance with standard practice for TRIDYNE™ VS components.

## 11.0 HOW SUPPLIED

**STERILE:** TRIDYNE™ VS is supplied sterile, single use with total reconstituted component volume of 4 mL per unit.

## 12.0 STORAGE

TRIDYNE™ VS should be stored between 2°C and 8°C (36°F to 46°F). Do not freeze.

## 13.0 SYMBOL DEFINITIONS

Symbol	Definition
	Catalogue Number
	Batch Code
	Use By
	Sterilized using irradiation
	Sterilized using Ethylene Oxide

	Consult instructions for use
	Do not use if package is damaged
	Do not reuse
	Temperature limitation. Storage should be refrigerated 2°C to 8°C (36°F to 46°F)
	Non-Pyrogenic
	Manufacturer
Rx Only	Prescription use only
	Biohazard

	<b>Applicator Kit</b>
	<b>Chemistry Kit</b>



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