Baxter

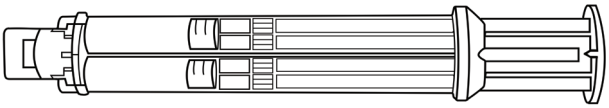
PREVELEAK Surgical Sealant

Instructions for Use

DEVICE DESCRIPTION

PREVELEAK Surgical Sealant (PREVELEAK) is a sealant developed to seal suture holes formed during surgical repair of the circulatory system and to reinforce sutured anastomoses. When applied, PREVELEAK creates an elastic biocompatible gel that seals suture holes or gaps formed between synthetic grafts or patches and native vessel anastomosis. PREVELEAK adheres to the native tissues as well as synthetic materials, including Polytetrafluoroethylene (PTFE) and Dacron grafts, and facilitates sealing along anastomotic closure lines. After application, PREVELEAK is a natural golden color and stays soft and flexible. Animal studies showed significant absorption by 12 months with biodegradation that continues beyond 24 months.

PREVELEAK is provided in a double-barreled, 2.5 mL, 4 mL, and 5 mL syringe assembly, containing equal volumes of purified bovine serum albumin (BSA) and polyaldehyde. PREVELEAK is supplied in a double pouch, with 2 delivery tips.



PREVELEAK is ready to use once the pouch is opened, the syringe cap removed, the delivery tip is attached and the tip is primed. When the plunger is depressed, the two components are thoroughly mixed as they pass through the delivery tip.
After application, allow the sealant to remain undisturbed for at least 60 seconds before unclamping and exposing the anastomosis to arterial pressure. PREVELEAK is applied as a viscous liquid that gels within approximately 10-15 seconds. PREVELEAK is terminally sterilized by e-beam irradiation and is provided in a double pouch with two delivery tips. Additional sterile delivery tips are available separately. PREVELEAK is provided for single-use only.

INDICATIONS

PREVELEAK Surgical Sealant is indicated for use in vascular and cardiac reconstructions (excluding application to arterial and venous grafts used in coronary artery bypass graft surgery) to achieve adjunctive hemostasis by mechanically sealing areas of potential leakage.

CONTRAINDICATIONS

- Not for use in patients with known allergies to materials of bovine or shellfish origin.
- Not for intravascular use.
- Not for cerebrovascular repair or cerebrospinal leak repair.

WARNINGS

- Do not use as a substitute for sutures or staples.
- Open lumen procedures require protection of the lumen.
- Avoid exposure to nerves including the sinoatrial node, and the atrial ventricular nodes.
- Do not use in the presence of obvious infection and use with caution in contaminated areas of the body.
- Do not allow either the uncured or polymerized form to come into contact with circulating blood.
- PREVELEAK contains a material of animal origin that may be capable of transmitting infectious agents.
- Repeated use of PREVELEAK in subsequent surgeries has not been studied. Hypersensitivity reactions were not seen using PREVELEAK, but hypersensitivity of BSA has been reported.
- Do not use PREVELEAK on arterial and venous grafts during coronary artery bypass graft surgery. PREVELEAK may reduce the vasoreactivity of vascular (i.e., internal mammary artery [IMA], radial artery [RA], and saphenous vein [SV]) grafts used in coronary artery bypass graft surgery at the site of application. Please refer to the Ex Vivo Vasoreactivity Study on page 9 for additional information.

PRECAUTIONS

- Avoid contact with skin or other tissue not intended for application.
- Safety and effectiveness of PREVELEAK in minimally invasive procedures have not been established.
- Do not use blood saving devices when suctioning excess PREVELEAK from the surgical field.
- PREVELEAK syringe and delivery tips 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 syringe. Avoid tissue contact with material expelled from delivery tip during priming.
- Avoid pausing more than 10-15 seconds between priming and application to prevent polymerization within the delivery tip.
- Use of PREVELEAK in pediatric or pregnant patients has not been studied.
- Minimize use in patients with abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism). Polyaldehyde treated tissue can have an enhanced propensity for mineralization.
- Evidence of cytotoxicity was observed during cell culture-based laboratory assays and is believed to be due to the polyaldehyde component of the product. No evidence of cytotoxicity was observed in animal or clinical studies.

CLINICAL STUDIES

The applicant performed a pivotal clinical study to establish a reasonable assurance of safety and effectiveness of the PREVELEAK Surgical Sealant when used during vascular surgical procedures to provide adjunctive hemostasis. This study was a prospective, randomized, controlled trial conducted in the United States under IDE #G070211. Data from this clinical study were the primary basis for the original Premarket Approval (PMA) decision (P100030; approved 01 March 2013) for use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage. In addition, data collected from a multi-center, non-randomized clinical study in Europe were also provided and considered in support of this PMA.

As cardiac surgical procedures also carry a high risk of perioperative bleeding, the applicant completed a prospective, multi-center, single-arm study to establish reasonable assurance of safety and effectiveness of the PREVELEAK Surgical Sealant when used during cardiac reconstruction. Data from this clinical study were the primary basis for the PMA Panel-Track Supplement approval decision (P100030/S008) for use of the PREVELEAK Surgical Sealant in vascular and cardiac reconstructions (excluding application to vascular grafts used in coronary artery bypass graft surgery) to achieve adjunctive hemostasis by mechanically sealing areas of leakage. Summaries of the clinical studies are presented below.

US Vascular Study

A. Study Design

Subjects were treated between October 2008 and December 2009. The database for this PMA reflected data collected through March 2010 and included 217 subjects. There were 11 investigational sites. A maximum of 12 mL PREVELEAK was studied in a single subject.

The study was a prospective, multi-center, two-arm, randomized clinical study conducted to evaluate the safety and effectiveness of the PREVELEAK Surgical Sealant versus a control in sealing suture lines at the anastomosis between native vessels and synthetic (e.g., PTFE/Dacron) vascular grafts or patches used during open vascular reconstruction, vascular repair or hemodialysis access. Subjects were randomly assigned 1:1 to either receive PREVELEAK or the control device (Gelfoam Plus [Gelfoam/thrombin], a legally marketed alternative with a similar intended use), just prior to the time it was administered, for all treatment sites during the surgical procedure. All subjects were followed for 3 months following treatment.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who met the following key inclusion criteria:

a. The subject was ≥ 18 years old.
b. The subject must have been scheduled for the surgical placement of a PTFE or Dacron vascular graft or patch for large vessel repair/arterial reconstruction or hemodialysis access or arteriotomy.
c. The subject had no child bearing potential or had a negative serum or urine pregnancy test within 7 days of the index procedure.
d. The subject was willing and able to be contacted for the follow up visits at 6 weeks (± 7 days) and 3 months (± 7 days).
e. The subject or guardian provided written informed consent using a form that was reviewed and approved by the Institutional Review Board.

Patients were not permitted to enroll in the study if they met any of the following key exclusion criteria:

a. The subject had a known hypersensitivity or contraindication to heparin, bovine or seafood products.
b. The subject had a history of bleeding diathesis or coagulopathy, or might have refused blood transfusions.
c. The subject was currently enrolled in this, or another investigational device or drug trial that had not completed the required follow-up period.

2. Follow-Up Schedule

All subjects were examined during their hospital stay, and were scheduled to return for follow-up examinations at 6 weeks (± 7 days) and at 3 months (± 7 days) post-operatively. Adverse events (AEs) and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, the primary endpoint was the cumulative incidence of significant bleeding, infection, neurological deficit or immune/inflammatory allergic response observed within 6 weeks post treatment. Additional safety endpoints included AE assessment at the following time points: in-hospital, 6 weeks and 3 months post-surgery.

With regards to effectiveness, the primary endpoint was immediate sealing, as evidenced by no bleeding after clamp release during the surgical procedure. Additional effectiveness endpoints included sealing at intervals of 1, 3, 5 and 10 minutes after clamp release, measured as both bleeding status and time to sealing; device malfunctions and ability to deliver the sealant; and type and quantity of additional hemostatic agents used during the procedure.

B. Accountability of PMA Cohort

Of the 217 subjects enrolled in the PMA study, 91% (197/217) in both control and treatment arms were available for analysis at the completion of the study, the 3-month post-operative visit. The subject accountability is provided in **Table 1**.

Table 1: Subject Accountability

	PREVELEAK (N = 110)	Control (N = 107)
Randomized	110 (100%)	107 (100%)
Treated	110 (100%)	107 (100%)
Discharged	110 (100%)	107 (100%)
Completed 6-Week Follow-Up	102 (92.7%)	100 (93.5%)
Completed 3-Month Follow-Up	100 (90.9%)	97 (90.7%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral vascular sealant study performed in the US. **Table 2** depicts the key patient demographics.

Table 2: Patient Demographics

	PREVELEAK (N = 110)	Control (N = 107)	p-value
Age (Years)			0.7415
Mean ± SD	66.2 ± 12.3	65.7 ± 12.3	
Range	20.8 – 86.6	26.2 – 95.1	
Gender			
Female	37.3%	34.6%	0.6793
Male	62.7%	65.4%	
Race/Ethnicity			
White	68.9%	69.2%	0.3053
Black	30.2%	27.9%	
Hawaiian/Pacific Islander	0.9%	0.0%	
Asian	0.0%	2.9%	
Hispanic/Latino	11.0%	10.3%	0.8622*
Body Mass Index (kg/m^2)			
Mean ± SD	28.8 ± 6.5	28.1 ± 7.2	0.4874
Range	14.5 – 49.3	17.9 – 59.3	

*Hispanic/Latino v. Non-Hispanic/Latino

The surgical procedures during which the PREVELEAK product was used are described in **Table 3.**

Table 3: Surgical Procedure Characteristics

	PREVELEAK (N=110 Subjects, 167 sites)	Control (N=107 Subjects, 164 sites)	Difference (95% C.I.)	p-value
Type of Surgical Procedure				
Aortic Procedures	10.9% (12/110)	14.0% (15/107)	-3.1% (-11.9, 5.7)	0.7156
Extremity Bypass Procedures	18.2% (20/110)	17.8% (19/107)	0.4% (-9.8, 10.6)	
Carotid Procedures	27.3% (30/110)	19.6% (21/107)	7.7% (-3.6, 18.9)	
Hemodialysis Access Grafting	22.7% (25/110)	24.3% (26/107)	-1.6% (-12.9, 9.7)	
Other	20.9% (23/110)	24.3% (26/107)	-3.4% (-14.5, 7.7)	
Type of Graft				
PTFE	67.7% (113/167)	62.8% (103/164)	4.9% (-5.4, 15.1)	0.3532
Dacron	32.3% (54/167)	37.2% (61/164)	-4.9% (-15.1, 5.4)	
Diameter of Graft (mm)				
Mean ± SD (N)	8.2 ± 4.0 (128)	8.6 ± 4.9 (131)		
Range (min, max)	(4.0, 28.0)	(3.0, 34.0)		
% of Grafts = Patch	23.4% (39/167)	19.5% (32/164)		
Number of anatomical sites treated				
One	53.6% (59/110)	54.2% (58/107)		
Two	40.9% (45/110)	38.3% (41/107)		
Three	5.5% (6/110)	7.5% (8/107)		

There were no statistically significant differences between the two randomized treatment groups with respect to basic demographics, surgical procedure performed or the type of graft utilized.

D. Safety and Effectiveness Results

1. Safety Results

The primary analysis of safety was based on the total cohort of 217 subjects who were evaluated at 6 weeks post-procedure. As indicated in **Table 4**, there were no statistically significant differences between the treatment and control groups with regards to any of the primary safety endpoints treated individually, as listed in **Table 4.** The difference between the two groups with respect to the cumulative incidence of safety measures, i.e., the incidence of subjects having 1 or more safety endpoints occurring within 6 weeks, was statistically significant (46.4% PREVELEAK compared to 59.8% control, $p < 0.05$).

Table 4: Primary Safety Endpoint Events through 6 Weeks

Safety Measure Within 6 Weeks Post-Treatment	PREVELEAK (N=110)	Control (N=107)	Difference (95% C.I.)	p-value
Significant Bleeding	35.5% (39/110)	45.8% (49/107)	-10.3% (-23.3, 2.7)	0.1209
Infection	14.8% (16/108)	23.6% (25/106)	-8.8% (-19.3, 1.7)	0.1031
Neurological Deficit	5.6% (6/108)	3.8% (4/105)	1.8% (-3.9, 7.4)	0.7482
Immune/Inflammatory Allergic Response	0% (0/108)	0.9% (1/106)	-0.9% (-2.8, 0.9)	0.4953
Cumulative Incidence of Safety Measures	46.4% (51/110)	59.8% (64/107)	-13.5% (-26.6, -0.3)	0.0472

The incidence of infections occurring within 6 weeks post-treatment was 14.8% for the PREVELEAK group compared to 23.6% for the Control group ($p = 0.1031$). Based on the protocol definition, infections include all instances where the subject's white blood cell count was 20% elevated from baseline, or where there was a positive blood or wound culture sufficient to cause the clinical investigator to take action. Therefore, all instances where antibiotics were required to treat an AE were included in this classification. The incidence of infections classified as serious adverse events (SAEs) occurring within 6 weeks post-treatment was 6.5% (7/108) for the PREVELEAK group compared to 16.0% (17/106) for the Control group. This difference was statistically significant ($p = 0.0268$).

Adverse effects that occurred in the pivotal study:

The SAEs that occurred in this study are presented in **Table 5** and **6.** There were no significant differences between the two randomized groups with respect to the prevalence of other SAEs potentially associated with vascular procedures occurring within 6 weeks. No differences in SAEs (infection, thrombosis/thromboembolism) or deaths were observed between 6 weeks and 3 months post-treatment.

Table 5: Serious Adverse Events through 6 Weeks

Serious Adverse Event	PREVELEAK (N=110)	Control (N=107)	Difference (95% C.I.)	p-value
Death	3.6% (4/110)	0.9% (1/107)	2.7% (-1.2, 6.7)	0.3694
Hypotension	2.7% (3/110)	0.0% (0/107	2.7% (-0.3, 5.8)	0.2467
Thrombosis/ Thromboembolism	1.8% (2/110)	0.0% (0/107)	1.8% (-0.7, 4.3)	0.4978
Ischemia	1.8% (2/110)	0.9% (1/107)	0.9% (-2.2, 4.0)	1.0000
Respiratory Failure/ Dysfunction	1.8% (2/110)	0.9% (1/107)	0.9% (-2.2, 4.0)	1.0000
Steal Syndrome	1.8% (2/110)	0.0% (0/107)	1.8% (-0.7, 4.3)	0.4978
Myocardial Infarction	0.9% (1/110)	0.0% (0/107)	0.9% (-0.9, 2.7)	1.0000
Pleural Effusion	0.0% (0/110)	0.9% (0/107)	-0.9% (-2.8, 0.9)	0.4931

A total of 7 deaths were reported with 6 deemed related to the subjects' underlying condition and 1 due to natural causes

Table 6: Serious Adverse Events - 6 Weeks through 3 Months

Serious Adverse Event	PREVELEAK (N=110)	Control (N=107)	Difference (95% C.I.)	p-value
Infection	2.7% (3/110)	1.9% (2/107)	0.9% (-3.1, 4.8)	1.0000
Thrombosis/ Thromboembolism	0.9% (1/110)	0.9% (1/107)	0.0% (-2.6, 2.5)	1.0000
Death	0.9% (1/110)	0.9% (1/107)	0.0% (-2.6, 2.5)	1.0000

2. Effectiveness Results

The primary analysis of effectiveness, a comparison of immediate suture line sealing, was conducted on the 331 anastomotic sites treated as part of the study. As indicated in **Table 7**, the difference in suture line sealing between the 2 groups was statistically significant, indicating superior sealing in the PREVELEAK group. This effectiveness analysis was also conducted on a per-patient basis, with no change in the results or conclusions.

Table 7: Primary Effectiveness Analysis: Immediate Suture Line Sealing

Parameter	PREVELEAK (N = 167)	Control (N = 164)	Difference (95% C.I.)	Conclusion
Immediate Suture Line Sealing	60.5% (101/167)	39.6% (65/164)	20.8% (10.3, 31.4)	PREVELEAK is Superior to Control

A significantly higher percentage of PREVELEAK sites (n=167) achieved immediate sealing compared to the control group (n=164) when PTFE grafts were used for the bypass procedure (62.8% vs 34.0%, respectively), while no such difference was observed for Dacron grafts (**Table 8**). In addition, no statistically significant difference in immediate sealing between the PREVELEAK and control groups was observed during aortic or carotid procedures, while immediate sealing was significantly higher for the PREVELEAK sites in extremity bypass, hemodialysis access grafting procedures, and all other types of vascular procedures, as seen in **Table 9**. It is important to note that the study was not designed to be powered for these types of comparisons.

Table 8: Primary Effectiveness by Type of Graft

Type of Graft	% of Sites with No Bleeding on Clamp Release			
	PREVELEAK (N=167)	Control (N=164)	Difference (95% C.I.)	p-value
PTFE	62.8% (71/113)	34.0% (35/103)	28.9% (16.1, 41.6)	<0.0001
Dacron	55.6% (30/54)	49.2% (30/61)	6.4% (-11.9, 24.6)	0.4946

Table 9: Primary Effectiveness by Surgical Procedure

Surgical Procedure	% of Sites with No Bleeding on Clamp Release			
	PREVELEAK (N=167)	Control (N=164)	Difference (95% C.I.)	p-value
Aortic Procedures	77.3% (17/22)	70.0% (21/30)	7.3% (-16.7, 31.3)	0.5591
Extremity Bypass Procedures	62.5% (20/32)	26.7% (8/30)	35.8% (12.8, 58.9)	0.0046
Carotid Procedures	30.0% (9/30)	38.1% (8/21)	-8.1% (-34.6, 18.4)	0.5461
Hemodialysis Access Grafting	69.6% (32/46)	32.6% (14/43)	37.0% (17.7, 56.3)	0.0005
Other Vascular Procedures	62.2% (23/37)	35.0% (14/40)	27.2% (5.7, 48.7)	0.0172

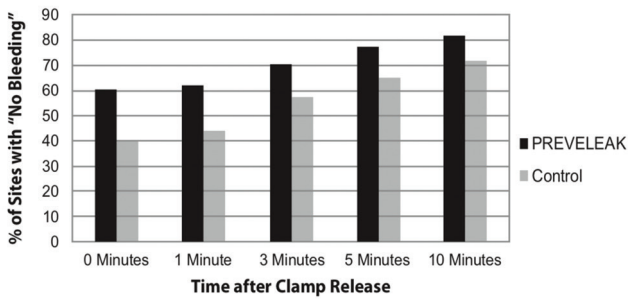
a. Bleeding Status through 10 Minutes

As a secondary endpoint, bleeding status was recorded for each treatment site immediately following clamp release, and at 1, 3, 5 and 10 minute intervals following clamp release. At each time point, the clinical investigator recorded either "Bleeding" or "No Bleeding." The percent of treated sites achieving hemostasis at each time point is presented in **Table 10** and **Figure 1.**

Table 10: Bleeding Status at 0, 1, 3, 5 and 10 Minutes

	% of Sites with "No Bleeding"		
Time After Clamp Release	**PREVELEAK (N=167)**	**Control (N=164)**	**Difference (95% C.I.)**
Immediate (0 Minutes)	60.5% (101/167)	39.6% (65/164)	20.8% (10.3, 31.4)
1 Minute	62.3% (104/167)	43.9% (72/164)	18.4% (7.8, 28.9)
3 Minutes	70.7% (118/167)	57.3% (94/164)	13.3% (3.1, 23.6)
5 Minutes	77.2% (129/167)	65.2% (107/164)	12.0% (2.3, 21.7)
10 Minutes	82.0% (137/167)	72.0% (118/164)	10.1% (1.1, 19.1)

Figure 1
Bleeding Status at 0, 1, 3, 5 and 10 Minutes



At 10 minutes, there was no statistically significant difference in bleeding between the PREVELEAK control groups with respect to the type of graft used or the type of procedure performed, as seen in **Tables 11** and **12**.

Table 11: Bleeding Status at 10 Minutes by Type of Graft

Type of Graft	% of Sites with "No Bleeding" at 10 Minutes			
	PREVELEAK (N=167)	**Control (N=164)**	**Difference (95% C.I.)**	**p-value**
PTFE	83.2% (94/113)	72.8% (75/103)	10.4% (-0.7, 21.4)	0.0650
Dacron	79.6% (43/54)	70.5% (43/61)	9.1% (-6.6, 24.8)	0.2601

Table 12: Bleeding Status at 10 Minutes by Surgical Procedure

Surgical Procedure	% of Sites with "No Bleeding" at 10 Minutes			
	PREVELEAK (N=167)	**Control (N=164)**	**Difference (95% C.I.)**	**p-value**
Aortic Procedures	95.5% (21/22)	80.0% (24/30)	15.5% (-1.3, 32.2)	0.2165
Bypass-Extremities	71.9% (23/32)	63.3% (19/30)	8.5% (-14.7, 31.8)	0.4721
Carotid Procedures	70.0% (21/30)	57.1% (12/21)	12.9% (-13.9, 39.6)	0.3444
Hemodialysis Access Grafting	93.5% (43/46)	83.7% (36/43)	9.8% (-3.4, 22.9)	0.1876
Other	78.4% (29/37)	67.5% (27/40)	10.9% (-8.8, 30.5)	0.2842

b. Time to Sealing through 10 Minutes

Time to sealing refers to the time the incision site was completely sealed, i.e., the last time point in which bleeding status equaled "No Bleeding" for each treatment site.

Kaplan-Meier methods were employed to summarize the cumulative time to sealing for all treated sites and compare the results between treatment groups. Censored observations include treatment sites where the clinical investigator intervened and used additional methods to achieve hemostasis prior to 10 minutes after clamp release. Among the 167 sites treated in the PREVELEAK group, 56.6% were sealed at 0 minutes, 62.7% at 1 minute, 71.3% at 3 minutes, 78.7% at 5 minutes, and 85.5% at 10 minutes after clamp release. Among the 164 sites treated in the Control group, 36.6% were sealed at 0 minutes, 44.1% at 1 minute, 58.2% at 3 minutes, 68.1% at 5 minutes, and 76.5% at 10 minutes after clamp release. Time to sealing was significantly better for PREVELEAK compared to the Control group ($p < 0.0005$) (**Figure 2** and **Table 13**).

Figure 2: Cumulative Time to Sealing – Kaplan Meier Results

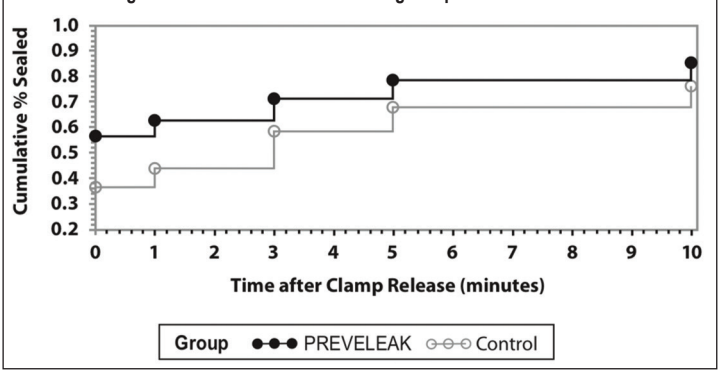


Table 13: Cumulative Time to Sealing – Kaplan Meier Results

	Time Period after Clamp Release				
	0 minutes	1 minute	3 minutes	5 minutes	10 minutes
PREVELEAK Group					
# Sites at beginning of Interval	167	72	62	43	32
# Censored Prior to Interval	1	0	6	0	4
# at Risk	166	72	56	43	28
# sealed	94	10	13	11	9
% Sealed	56.6	62.7	71.3	78.7	85.5
Standard error (%)	3.9	3.8	3.6	3.3	2.9
Control Group					
# Sites at beginning of Interval	164	104	90	62	45
# Censored Prior to Interval	0	2	7	3	3
# at Risk	164	102	83	59	42
# sealed	60	12	21	14	11
% Sealed	36.6	44.1	58.2	68.1	76.5
Standard error (%)	3.8	3.9	3.9	3.8	3.5

Wilcoxon Test between Groups, p-value = 0.0004

c. Surgery and Hospitalization Data

The total surgery time was defined as the time the initial incision was made to the time the dressings were placed. The average surgery time was 3.2 ± 1.4 hours for the PREVELEAK group, which was statistically significantly less than the 3.8 ± 2.2 hours for the Control group ($p \leq 0.01$). The total hospitalization time was defined as the number of days between the initial study procedure and the date of hospital discharge. The average hospitalization time was 4.1 ± 5.5 days for the PREVELEAK group and 5.4 ± 7.0 days for the Control group, which does not represent a statistically significant difference (**Table 14**).

Table 14: Procedural Data for all Treated Sites

Procedural Data	PREVELEAK (N=110 pts / 167 sites)	Control (N=107 pts / 164 sites)	Difference (95% C.I.)	p-value
Time between Clamp release and Bleeding Stopped (min)				
Mean ± SD (N)	5.1 ± 15.1 (166)	5.3 ± 7.6 (164)	---	0.0008[1]
Median	0.0	3.0		
Range (min, max)	(0, 132)	(0, 40)		
Total Surgery Time (hrs)				
Mean ± SD (N)	3.2 ± 1.4 (110)	3.8 ± 2.2 (106)	-0.7 (-1.2, -0.2)	0.0085
Range (min, max)	(1.0, 7.7)	(1.0, 11.1)		
Total Hospitalization Time (days)				
Mean ± SD (N)	4.1 ± 5.5 (110)	5.4 ± 7.0 (107)	-1.3 (-3.0, 0.4)	0.1273
Range (min, max)	(0, 42)	(0, 43)		

[1]Wilcoxon, 2 sample test.

EU Cardiac Study

A. Study Design

The study included 44 patients from 3 European Union (EU) investigational sites. A maximum of 28 mL of PREVELEAK was studied in a single patient. Patients were treated from June to December 2013.

The study was a prospective, open-label, single-arm, multicenter study to evaluate the safety and effectiveness of PREVELEAK sealing suture lines at proximal and distal coronary anastomoses, aortic anastomoses, cannulation sites, and access incision sites on the aorta, atrium, and ventricle. All patients were followed for 3 months after treatment.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who met the following key inclusion criteria:

a. The subject was ≥ 18 years old.
b. The subject had a known indication that required cardiac surgery and determined to be at risk for poor hemostasis.
c. The subject had no child bearing potential or negative serum or urine pregnancy test within 7 days of the index procedure.
d. The subject was willing and able to be contacted for the follow up visits at 6 weeks (± 7 days) and 3 months (± 7 days).
e. The subject or guardian must have provided written informed consent using a form that was reviewed and approved by the Institutional Review Board.

Patients were not permitted to enroll in the study if they met any of the following key exclusion criteria:

a. The subject had a known hypersensitivity or contraindication to heparin, bovine or seafood products.
b. The subject had a history of bleeding diathesis or coagulopathy, or might refuse blood transfusions.
c. The subject was currently enrolled in this, or another investigational device or drug trial that had not completed the required follow-up period.

2. Follow-Up Schedule

All patients were examined during their hospital stay, and were scheduled to return for follow-up examinations at 6 weeks (± 7 days) and at 3 months (± 7 days) post-operatively AEs and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, the primary endpoint was the cumulative incidence of significant bleeding, infection, neurological deficit or immune/inflammatory allergic response observed within 6 weeks post-treatment. Additional safety endpoints included AE assessment at the following time points: in-hospital, 6 weeks and 3 months post-surgery.

With regards to effectiveness, the primary endpoint was immediate sealing of the suture/staple line at the point of use upon release of the clamps or taking the patient off-pump as evidenced by an absence of clinically significant bleeding (minor oozing was not considered clinically significant) as determined by the investigator using the PREVELEAK device.

Additional endpoints included sealing at intervals of 1, 3, 5 and 10 minutes after clamp release or taking the patient off-pump. Re-operation, intra-operative complications, mortality rates, device usage parameters were also assessed, inclusive of exposure to blood replacement products, and peri-/post- operative medications.

B. Accountability of Study Cohort

Forty-six subjects were enrolled in the study. Two subjects withdrew informed consent prior to undergoing a qualifying surgical procedure. The remaining 44 subjects all underwent a surgical procedure, had PREVELEAK sealant applied to at least one site, and were included in both safety and efficacy analyses. The subject accountability is provided in **Table 15.**

Table 15: Subject Accountability

	PREVELEAK (N = 46)
Treated	44 (95.7%)
Completed 6-Week Follow-Up	42 (91.3%)
Completed 3-Month Follow-Up	41 (89.1%)

C. Study Population Demographics and Medical History

As shown in **Table 16**, of the 44 subjects treated with PREVELEAK, 70.5% were male. The mean age was 64.6 years and average BMI was 28.4 kg/m2. Hypertension (n = 35/44, 79.5%) was the most prevalent concomitant condition. Thirty-two of 44 subjects (72.7%) received anticoagulants (low molecular weight heparin or vitamin K antagonists) and/or antiplatelet medications (cyclooxygenase or P2Y12 inhibitors) intra-operatively or ≤ 5 days prior to surgery.

Table 16: Subject Demographics and Medical History

	PREVELEAK (N = 44)
Age (years)	
Mean ± SD	64.6 ± 10.5
Range (min, max)	(42, 84)
Gender	
Female	29.5%
Male	70.5%
Body Mass Index (kg/m2)	
Mean ± SD	28.4 ± 4.1
Range (min, max)	(18.3, 35.3)
Medical History	
Hypertension	79.5%
Diabetes	31.8%
History of Thrombosis	2.3%

A total of 63 cardiac surgical procedures were performed on the 44 subjects. PREVELEAK was applied to 127 sites and approximately two-thirds of subjects (n = 29/44, 65.9%) had multiple (2 to 7) sites treated (**Table 17**). Distal anastomoses in coronary artery bypass graft (CABG) procedures were the most common application site (n = 60/127, 47.2%).

Grafts were used at 94 of 127 treatment sites (74.0%; **Table 17**). Most grafts (n = 85/94, 90.4%) were harvested from the subjects, with 54.2% (n = 51/94) obtained from a vein and 36.1% (n = 34/94) from an artery. All harvested grafts were used in CABG procedures. The 5 Dacron grafts were used for aortic aneurysm repair and the 4 prosthetic grafts were used for aortic root reconstruction (n = 2) and aortic aneurysm repair (n = 2).

Table 17: Surgical Procedure Characteristics

	PREVELEAK (N = 44 Subjects, 127 Sites)
Coronary Artery Bypass Graft	67.7% (86/127)
Aortic Valve Replacement	14.2% (18/127)
Mitral Valve Reconstruction	6.3% (8/127)
Aortic Aneurysm Repair	5.5% (7/127)
Tricuspid Valve Reconstruction	2.4% (3/127
Aortic Root Reconstruction	1.6% (2/127)
Cannulation Site	1.6% (2/127)
Aortic Valvuloplasty	0.8% (1/127)
Type of Graft	
Vein	40.2% (51/127)
Artery	26.8% (34/127))
Dacron	3.9% (5/127)
Prosthetic	3.1% (4/127)
No Graft Used	26.0% (33/127)

D. Safety and Effectiveness Results

1. Safety Results

Overall, 71 AEs were reported for 36 subjects. Most events were mild (n = 46/71, 64.8%) or moderate (n = 18/71, 25.4%) in severity and had resolved by the time of study termination (78.9%). The majority of the AEs occurred within the first 6 weeks following surgery (63/71; 88.7%), as anticipated for subjects undergoing cardiac surgery.

The primary safety measure was any instance of significant bleeding, infection, neurological deficit, or immune/inflammatory allergic response observed within 6 weeks post-treatment. The cumulative incidence of such events was 9 events in 8 subjects (n = 8/44, 18.2%); 1 subject experienced 2 events (**Table 18**). These events were considered by the investigators as not related to treatment with PREVELEAK and included 8 infections (sternal wound: 4, urinary: 2, respiratory: 1, and epidermal: 1) and 1 neurological deficit (transient confusion that began 2 days post-operatively and resolved after 1 day). All of the sternal wound infections were considered to be superficial.

Table 18: Primary Safety Endpoint Events Through 6 Weeks

Safety Measure Within 6 Weeks Post-Treatment	**PREVELEAK (N = 44)**
Significant Bleeding	0% (0/44)
Infection	18.2% (8/44)
Neurological Deficit	2.3% (1/44)
Immune/Inflammatory Allergic Response	0% (0/44)
Cumulative Incidence of Safety Measures	18.2% (8/44)

Serious Adverse Events

Eighteen serious adverse events were reported by 12 subjects. The most common serious adverse events were cardiac tamponade and heart block (Types II and III); they occurred in 3 subjects each.

One serious adverse event, spasm (or visual narrowing) of the distal left internal mammary artery (LIMA) graft applied to the left anterior descending coronary artery (LAD) during CABG after application of PREVELEAK was determined to be definitely procedure related (due to surgical instrument manipulation during CABG surgery) and possibly device related. There were no EKG changes, no change in cardiac movement, and no change in the color of the myocardium in the distribution of the LAD. Although the investigator could not determine if the vasospasm was due to the procedure alone or at least partly in response to the device, the sealant was removed intra-operatively as a precautionary measure. No bleeding occurred and no damage to the vascular surface was observed and the event resolved during the surgical procedure without sequelae.

SAEs occurring within 6 weeks and between 6 weeks and 3 months post-treatment are shown in **Tables 19 and 20**, respectively.

Table 19: Serious Adverse Events Through 6 Weeks

Serious Adverse Event	PREVELEAK (N = 44)
Cardiac Tamponade	0.07% (3/44)
Atrioventricular Block (Type III)	0.05% (2/44)
Sternal Instability	0.05% (2/44)
Asystole	0.02% (1/44)
Acute Renal Injury	0.02% (1/44)
Atrioventricular Block (Type 2)	0.02% (1/44)
Cardiac Arrest	0.02% (1/44)
Myocardial Infarction	0.02% (1/44)
Prolonged INR	0.02% (1/44)
Spasm of Coronary Artery Graft	0.02% (1/44)
Wound Healing Disorder	0.02% (1/44)
Wound Healing Infection	0.02% (1/44)

Table 20: Serious Adverse Events – 6 Weeks Through 3 Months

Serious Adverse Event	PREVELEAK (N = 44)
Atrial Fibrillation	0.02% (1/44)
Inflammatory Reaction	0.02% (1/44)

Additional endpoints included rates of re-operation (due to bleeding or tissue disruption at the site of sealant application), intra-operative complications, and 3-month mortality. There were no re-operations due to bleeding at PREVELEAK-treated sites. There were 2 intra-operative complications, both of which occurred in 1 subject who underwent a CABG procedure. One of the events, spasm of the arterial graft after application of the sealant, is described above in the SAE section. The second event, (tooth luxation during intubation; mild severity) was not considered related to application of the sealant.

One subject died 22 days after hospital discharge due to cardiac arrest, possibly due to sepsis. The subject had a history of coronary artery disease, chronic obstructive pulmonary disease, and diabetes mellitus. The death was deemed by the investigator as unrelated to PREVELEAK.

2. Effectiveness Results

The primary effectiveness endpoint of immediate sealing was achieved at all sites in 42 of 44 subjects (95.5%) and at 125 of 127 treatment sites (98.4%) overall (**Table 21**). One hundred percent of the CABG anastomoses (n = 86/86) and atrium/ventricle incision sites (n = 11/11) and 93.3% of the aortic sites (n = 28/30) met the primary endpoint. There were 2 primary endpoint failures in 2 subjects. In 1 subject, surgical sealant was applied to a total of 4 hemostasis sites, with 3 sites at CABG distal anastomoses and 1 at the ascending aortic access incision site. The failure occurred at the aortic site, where brisk bleeding was observed requiring additional sutures. The other primary endpoint failure was due to a procedural error: PREVELEAK was applied after instead of before clamp release at an aorta-to-graft anastomosis during aortic aneurysm repair.

Table 21: Primary Effectiveness Analysis by Type of Procedure: Immediate Suture Line Sealing

Procedure	Number of Surgical Sealant Application Sites		
	Total Number of Application Sites (N)	Primary Endpoint Failure (%, n/N)	Primary Endpoint Success (%, n/N)
CABG	86	0% (0/86)	100% (86/86)
Valve Procedures	30	3.3% (1/30)	96.7% (29/30)
Other*	11	9.1% (1/11)	90.9% (10/11)
All	127	1.6% (2/127)	98.4% (125/127)

CABG = coronary artery bypass graft

*Other procedures included aortic aneurysm repair, aortic root reconstruction, and cannulation

Summary of Non-clinical Studies

Ex Vivo Vasoreactivity Study

Based on the single incident of LIMA spasm in the EU Cardiac Study (as described above in the SAE section), an ex vivo study was conducted to explore possible spontaneous vasoconstriction and vasoreactivity to constrictors and dilators after the application of PREVELEAK to the abluminal surface of isolated IMA, RA, and SV vascular rings.

A. Study Design

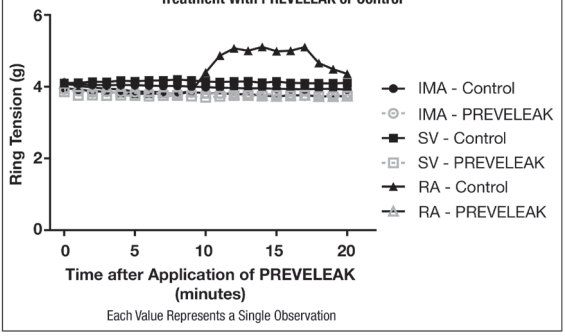
Harvested vessels discarded from patients undergoing CABG procedures were sectioned into cylindrical rings approximately 3 mm in length. The rings were suspended between 2 hooks in a tissue bath, allowed to equilibrate, and slowly adjusted to a baseline tension (2.0 g and 4.0 g). PREVELEAK was applied circumferentially to the abluminal surface of rings of each vessel type. After equilibration, the rings were exposed to potassium chloride (KCl) for 10 minutes to achieve maximal constriction. After a wash out period, the ring tension was

readjusted to the previously applied baseline tension. Control and PREVELEAK-treated rings were exposed to increasing concentrations of the thromboxane analog U46619 and rings remained maximally constricted for 10 minutes at the highest concentration of U46619. Constricted rings were then treated with increasing concentrations of the dilator adenosine diphosphate (ADP). Vessel rings were then washed and returned to baseline tensions and exposed to increasing concentrations of phenylephrine and rings remained maximally constricted for 10 minutes at the highest concentration of phenylephrine. After 10 minutes, the constricted rings were exposed to increasing concentrations of the dilator sodium nitroprusside (SNP).

B. Results

PREVELEAK had no effect on baseline tension when applied to IMA, SV, or RA rings. As shown in **Figure 3**, there was no evidence of spontaneous vasoconstriction with the application of PREVELEAK. Note that the only incidence of spontaneous constriction was in control RA rings.

Figure 3: Stability of Baseline Tension of Rings From the IMA, SV, and RA After Treatment With PREVELEAK or Control



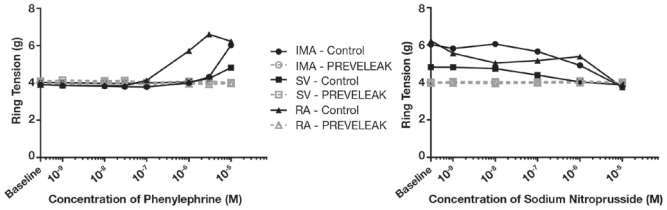
Each Value Represents a Single Observation

Control (IMA, SV, and RA) rings exposed to KCl produced an increase in ring tension. In contrast, rings (IMA, SV, and RA) treated with PREVELEAK showed no change. Control rings exposed to increasing concentrations of U46619 produced concentration-related increases in ring tension. After treatment with PREVELEAK, increasing concentrations of U46619 had no effect on ring tension, regardless of baseline tension.

After maximal contraction with U46619, control rings showed a concentration-dependent decrease in ring tension when exposed to ADP. Vessel rings treated with PREVELEAK failed to respond to increasing concentrations of ADP after exposure to U46619 preconstriction.

Control rings showed increases in ring tension with increasing concentrations of phenylephrine (**Figure 4**). In contrast, rings treated with PREVELEAK showed no change. After maximal precontraction-induced with phenylephrine, increasing concentrations of SNP produced dilation in control rings. Phenylephrine constricted rings treated with PREVELEAK showed no change in ring tension with increasing concentrations of SNP as shown in **Figure 4**.

Figure 4: Response to Increasing Concentrations of Phenylephrine Followed by SNP on IMA, SV, and RA Vascular Rings



Each Value Represents a Single Observation

Responses of rings with a baseline tension of 2.0 or 4.0 g were similar. In addition, although the magnitude of responses differed between vessel types and treatment, the directional presence of response (or absence of response) remained the same for tested vasoconstrictors (U46619 and phenylephrine) and dilators (ADP and SNP).

The results from this ex vivo study demonstrated that application of PREVELEAK did not likely cause vasoconstriction when applied to the abluminal surface of vascular rings from the IMA, RA, and SV. However, PREVELEAK blocked the responses to the vasoconstrictors and vasodilators tested. The mechanism responsible for this observation is unknown.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of this class of surgical sealants:

- Application of the sealant to tissue not targeted for the procedure
- Failure of the sealant to adhere to the tissue
- Hypersensitivity reaction such as swelling or edema at the application site
- Possible transmission of infectious agents from materials of animal origin
- Thrombosis and thromboembolism

Below is a list of the potential adverse effects (e.g., complications) associated with cardiac and vascular procedures:

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

For the specific AEs that occurred in the clinical studies, please see the Clinical Study section above.

Directions for Use

HOW SUPPLIED

Packaging contains 1 double-barreled syringe and 2 delivery tips.

- Additional delivery tips may be purchased separately.
- PREVELEAK and its accessories are not made with natural rubber latex.
- PREVELEAK syringe and delivery tips are for single patient use only. Do not re-sterilize.
- Discard unused material.
- Do not use if packages have been opened or damaged.
- Dispose of device following local regulations on disposal of medical waste.

STORAGE

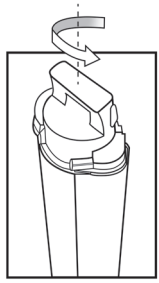
Store at 2°C(36°F) to 8°C(46°F)

NOTES:

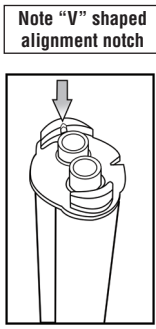
- In case of contact with eyes, flush with plenty of water and seek medical attention.
- Take special care when assembling and handling the device to prevent accidental discharge from the syringe.
- PREVELEAK polymerizes rapidly. Use sealant immediately after priming the delivery tip to avoid the tip becoming blocked and requiring replacement.

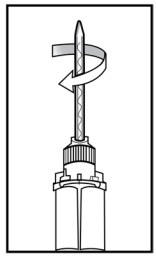
PREPARATION

1. Remove from box and allow PREVELEAK to reach room temperature prior to use.
2. Open the outer pouch and place the inner sterile pouch onto the sterile field.
3. Open the inner pouch and remove the double-barrel syringe and the delivery tips.
4. Hold the syringe by the barrel, cap-end upwards.



5. Remove the cap by turning 90° counterclockwise and pulling upwards, using a slight side to side rocking motion. Note how the cap attaches and detaches since the delivery tip is attached in the same manner.





6. Attach the delivery tip to the syringe as follows: Locate the small alignment tab on the hub-end of the delivery tip. Locate the corresponding V-shaped alignment notch in 1 of the two upper locking wings at the open end of the syringe. Align the tab in the notch and push delivery tip into place. Turn delivery tip 90° clockwise to lock the tip to the syringe.

Application Procedure:

7. Ensure that the application site is clamped and there is no active bleeding.
8. During an aortic dissection repair, the device is applied only to the exterior surface of the anastomoses (abluminally) and the lumen must be protected. Cardiotomy suction should be turned off before device application during CABG or aortic procedures to minimize potential entry into the lumen.
9. Prime the syringe by discarding the first 0.25 mL of sealant immediately prior to use. This ensures that fully mixed product in the proper proportions is delivered to the application site. PREVELEAK is now ready to be applied to the surgical site. Apply the sealant in a slow and steady manner over the top of the suture line with the delivery tip approximating the sutures.
10. After the application is complete, leave the clamps in place for at least 60 seconds before restoring circulation, applying irrigation, blotting with gauze or touching the sealant.
11. Prior to restoring circulation, carefully use blunt dissection to ease away any sealant attached to the clamps. Gently remove the clamps without disturbing the sealant at the application site.
12. Do not manipulate the synthetic graft or patch.

Explanation of Symbols Used in Labeling

	Consult instructions for use		Manufacturer
	Use-by date		Temperature limit
	Do not re-use		Not made with natural rubber latex
	Sterilized using irradiation	Rx Only	Caution: Federal Law (USA) restricts this device to sale by or on the order of a licensed healthcare practitioner
	Catalog Number		Do not use if package is damaged
	Batch code		Do not resterilize

Manufactured By:
Baxter Healthcare Corporation
835 Maude Ave
Mountain View, CA 94043
USA
Phone: 1-888-229-0001

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