LABELING

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

A. General Information

Premarket Approval Application (PMA) Number: P030039
Date Filed: September 9, 2003
Date Approved:

Device Generic Name:	Polymerizing Sealant
Device Trade Name:	CoSeal Surgical Sealant (CoSeal)
Applicant Name:	Baxter Healthcare Corporation
Applicant Address:	34175 Ardenwood Boulevard Freemont, CA 94303 USA
Contact Person:	Arlene Vidor Phone: (805) 372-3040 Fax: (805) 372-3042 Email: Arlene_vidor@baxter.com
Manufacturer Site Name, Address:	Cohesion Technologies 2500 Faber Place Palo Alto, CA 94303
PMA Number:	P030039

B. Indications for Use

CoSeal is indicated for use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage.

C. Center for Devices and Radiological Health Decision (CDRH)

This application includes by reference the data in PMA P010022 for the CoSeal Surgical Sealant by Cohesion Technologies, Inc approved on December 14, 2001. Cohesion Technologies, Inc. has given Baxter Healthcare Corporation, a license right to incorporate by reference the information contained in its approved PMA, P010022.

CoSeal Surgical Sealant will continue to be manufactured by Cohesion Technologies Inc., and will be distributed by Baxter Healthcare Corporation.

CDRH approval of the Baxter Healthcare Corporation, PMA is based on (1) the safety and effectiveness data contained in PMA P010022 and (2) the results of the FDA manufacturing facility of Cohesion on December 13, 2001. A summary of safety and effectiveness data for the CoSeal Surgical Sealant appears in Attachment.

Attached

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

A. General Information

Device Generic Name:	Polymerizing Sealant
Device Trade Name:	CoSeal Surgical Sealant (CoSeal)
Applicant Name:	Cohesion Technologies, Inc.
Applicant Address:	2500 Faber Place Palo Alto, CA 94303 USA
Contact Person:	Roxanne Dubois Phone: (650) 320-5534 Fax: (650) 320-5544 Email: rdubois@cson.com
Manufacturer Site Name, Address:	Cohesion Technologies 2500 Faber Place Palo Alto, CA 94303
Establishment Registration Number:	2953731
PMA Number:	P010022
IDE Number for Reference:	G990324
Marketing History:	CoSeal Surgical Sealant was approved to affix the CE mark and began commercial sale in the European Union on February 21, 2000 (EC Certificate No.: G1 00 02 28707 007).

B. Indications for Use

CoSeal is indicated for use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage.

C. Device Description

CoSeal Surgical Sealant (CoSeal) is a hydrogel that is designed to act as a vascular sealant. The hydrogel is formed when two synthetic derivatized polyethylene glycol (PEG) polymers are mixed together and applied to tissue. The hydrogel acts as a sealant by adhering to itself and to the tissues it contacts. The PEG polymers are separately supplied as powders in

syringes that are connected to their reconstitution buffers, which are contained in separate syringes. CoSeal is prepared by syringe-to-syringe mixing of the buffers with their corresponding powders resulting in two syringes, each containing a dissolved PEG. The dissolved PEGs are co-extruded during administration to the tissue site using a delivery system. The hydrogel forms within seconds after application and resorbs over several weeks.

The delivery systems are comprised of a syringe support, a syringe clip, and an applicator tip. All product-contacting components of the Delivery System are certified to have passed USP Class VI testing. By definition, USP Class VI materials have been tested and demonstrated to be biocompatible and non-toxic in accordance with the Systemic Injection Test, the Intracutaneous Test, and the Implantation Test.

D. Contraindications, Warnings, and Precautions

Contraindications

- There are no known contraindications for this device.

Warnings and Precautions

The Warnings and Precautions can be found in the product labeling.

E. Alternative Practices and Procedures

Alternative treatments include the use of hemostats/sealants composed of human collagen, fibrinogen and thrombin indicated for cardiac, general, orthopedic and hepatic surgeries. Bovine collagen gel hemostats with bovine thrombin are also available to control bleeding in cardiac, vascular and spinal surgery. To treat air leaks following lung surgery, and for use in neurosurgery, synthetic liquid polymer sealants are used in conjunction with an activating light source. Another treatment is available for use in the repair of aortic dissections using a bovine albumin/gluteraldehyde surgical adhesive.

F. Marketing History

CoSeal received the CE Mark in February 2000 and was introduced into European commercial distribution shortly thereafter, and was approved in Australia in 2001. CoSeal is indicated for use in sealing arterial and/or venous reconstructions. It has not been withdrawn from any market at any time in any country.

G. Potential and Observed Adverse Effects of the Device on Health

1. Observed Adverse Events

In a prospective, randomized, controlled multicenter trial, 148 patients were treated with CoSeal or the control (absorbable gelatin sponge/thrombin hemostat). Table 1 shows the overall adverse events reported for CoSeal treated and control patients for the 10 most commonly reported events. The results are similar between the two treatment groups and are representative of events expected from patients undergoing vascular surgery for vascular access and occlusive vascular disease.

There were two deaths in the study. One control patient died during the study due to cardiopulmonary arrest. A second control patient died of sepsis and carbon dioxide narcosis with respiratory arrest. Five weeks post treatment, this patient had surgery for a duodenal ulcer with hemorrhage.

Table 1: Adverse Events

Adverse Event	CoSeal (n=74)	Control (n=74)
Edema	14 (18.9%)	11 (14.9%)
Elevated Temperature ≥101F*	10 (13.9%)	8 (11.1%)
Erythema	10 (13.5%)	7 (9.5%)
Infection	8 (10.8%)	6 (8.1%)
Thrombosis	6 (8.1%)	8 (10.8%)
Occlusion	6 (8.1%)	7 (9.5%)
Hematoma	5 (6.8%)	3 (4.1%)
Anemia	3 (4.1%)	4 (5.4%)
Non-Healing Wound**	4 (5.4%)	2 (2.7%)
Bleeding***	4 (5.4%)	1 (1.4%)

* Temperature data was collected on 72 patients from each treatment group.

** The non-healing wound was not at the treatment site for 3 of the 6 patients (1 control, 2 CoSeal patients).

*** Bleeding was not at the treatment site for 3 of the 5 patients (3 CoSeal patients).

When evaluating the total adverse events reported in the study, there were 185 events in CoSeal treated patients and 151 in Control patients. This is a difference of 34 more events in the CoSeal group. In evaluating this difference, it was found that one CoSeal treated patient contributed 35 adverse events which represents more than the total difference between treatment groups. From the total of 336 events only two (both controls) were attributed to the treatment material by the attending surgeon. The remaining 334 events are not related to the treatment material in the opinion of the treating physicians. It is concluded that there was not an unexpected adverse event finding, either by event type or number, attributed to the use of CoSeal. The safe use of CoSeal for sealing peripheral vascular reconstructions is supported by the findings of this randomized controlled clinical study.

2. Potential Adverse Events that may Occur from the Use of CoSeal

- Hypersensitivity reaction such as swelling or edema at the application site
- Application of the adhesive to tissue not targeted for the procedure
- Failure of CoSeal to adhere to the tissue
- Thrombosis and thromboembolism

3. 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
- Stroke or cerebral infarction
- Thrombosis
- Vasospasm
- Vessel rupture and hemorrhage

H. Pre-clinical Studies

In biocompatibility tests conducted in accordance with ISO 10993 (Biological evaluation of medical devices, Part 1, Guidance on selection of tests, 1997), CoSeal was shown to be non-cytotoxic;; non-mutagenic; and non-clastogenic. Sensitization testing demonstrated that the material is a very mild skin sensitizer. The ability of CoSeal to seal suture holes was evaluated in three animal models to evaluate the product's effectiveness: a rabbit carotid defect model, a canine iliac graft model, and an acute large animal (ovine and bovine) model. Results showed CoSeal is biocompatible; effective at reducing the time to hemostasis and the amount of blood loss compared to controls; completely resorbed; and, effective at sealing a variety of soft tissue surface incisional lines, as well as, vascular graft suture lines.

A 30 day dosing toxicity study (rat intraperitoneal implant) showed no clinical signs of toxicity at 7.5ml/kg and 15 ml/kg. At doses of 30 ml/kg, urinalysis & urine chemistry showed an increase in urine volume, decreased urine specific gravity, and decreased concentrations of urinary analytes in at day 8, which resolved by day 15.

In vitro studies demonstrated that CoSeal forms a gel in <3 seconds; effectively seals suture holes; adheres to the treatment site; and is resorbed in <30 days. Summaries of the in vitro studies are summarized in Table 2, below.

TABLE 2: Summary of In Vitro Studies

Test Performed	Test Sample	Result
Setting Time	Final Product CoSeal Hydrogel	Gel Formed in < 3 Seconds
Gel Strength	Final Product: CoSeal Hydrogel	Test Site Sealed with No Leakage
Adherence	Final Product. CoSeal Hydrogel	CoSeal Remained Adherent and Prevented Leakage
Delivery System Performance	Final Product: CoSeal Hydrogel	Delivery System Performance was Acceptable
Degradation Study	Final Product: CoSeal Hydrogel	CoSeal is Resolved by Day 30.

I. Clinical Studies

Two multicenter clinical studies were conducted to investigate CoSeal for use in sealing peripheral arterial and/or venous reconstructions. The study design, endpoints, and results from these studies are summarized below.

1. US Multicenter Randomized Trial

Study Design and Objectives: A prospective, randomized, controlled multicenter trial was conducted to evaluate the safety and effectiveness of CoSeal versus an absorbable gelatin sponge/thrombin hemostat to seal anastomotic suture lines in patients undergoing placement of vascular grafts. One hundred and forty eight (148) patients were treated with CoSeal or the control at nine centers. This study was designed to evaluate whether the CoSeal success rate was equivalent to the success rate for the control. There were no reported unanticipated adverse effects related to CoSeal Surgical Sealant in this investigation.

Table 3: Patient Accountability		
	CoSeal	Control
Number Patients Treated	74	74
Number Patients with 1 site Treated	12	20
Number Patients with 2 Sites Treated	62	54
Total Number of Sites Treated	136	128

Table 4: Patient Demographics by Age and Gender		
	CoSeal (N=74)	Control (N=74)
Age (years)		
Mean ± s.d.	63 ± 13	61 ± 14
Median	64	63
Range	23 – 87	22 – 85
Males	41	37
Females	33	37
Surgical Procedure		
Bypass	29 (39%)	26 (35%)
AV-Shunt	43 (58%)	44 (59%)
Other	2 (3%)	4 (5%)

Primary Endpoint: The primary effectiveness outcome parameter measured was the cessation of bleeding (sealing) at a treatment site within 10 minutes.

Secondary Endpoint: The secondary measure of effectiveness was the *Time to Sealing* (the number of seconds from the time circulation is restored to the graft until the time bleeding has ceased at the site). Immediate sealing is defined as no bleeding when circulation was restored to the graft (immediate sealing = 0 seconds).

Table 5: Sites Achieving Complete Sealing All Treated Sites (Success/Total)		
	CoSeal	Control
Immediate (0 seconds)	64/136 (47%)	25/128 (20%)
Within 10 Minutes (cumulative)	117/136 (86%)	108/128 (84%)

Table 6: Patients Achieving Complete Sealing All Treated Patients (Success/Total)		
	CoSeal	Control
Immediate (0 seconds)	24/74 (32%)	12/74 (16%)
Within 10 Minutes (cumulative)	60/74 (81%	58/74 (78%)

Table 7: Sites Achieving Immediate Sealing by Surgical Group All Treated Sites* (Success/Total)		
	CoSeal	Control
Bypass Grafts	22/53 (42%)	5/45 (11%)
AV-Shunts	42/80 (53%)	18/79 (23%)

* Patch grafts not reported.

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Table 8: Patients Achieving Complete Sealing by Surgical Group All Treated Patients (Success/Total)*		
	CoSeal	Control
Bypass Grafts	20/29 (69%)	18/26 (69%)
AV-Shunts	40/43 (93%)	37/44 (84%)

* Patch grafts not reported.

Table 9: Sites Achieving Immediate Sealing by Degree of Pretreatment Bleeding All Treated Sites		
	CoSeal	Control
Oozing	50%	26%
Brisk	41%	3%

Table 10: Cumulative Percent of Treatment Sites with Complete Sealing over 10 Minutes All Treated Sites (Success/%)		
	CoSeal	Control
Immediate (0 seconds)	64 (47%)	25 (20%)
0-1 Minute	82 (60%)	41 (32%)
0-3 Minutes	100 (74%)	68 (53%)
0-5 Minutes	109 (80%)	89 (70%)
0-10 Minutes	117 (86%)	108 (84%)

Table 11: Cumulative Number of Patients with Complete Sealing over 10 Minutes All Treated Patients (Success/%)		
	CoSeal	Control
Immediate (0 seconds)	24 (32%)	12 (16%)
0-1 Minute	34 (46%)	19 (26%)
0-3 Minutes	48 (65%)	29 (39%)
0-5 Minutes	55 (74%)	42(57%)
0-10 Minutes	60 (81%)	58 (78%)

Multiple analyses were conducted to evaluate the effectiveness data by treatment site and by patient. These analyses demonstrated that the study objectives were met when the data was analyzed by patient as well as by site.

Inclusion and exclusion criteria were chosen to avoid gender bias. 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.

This multicenter study demonstrated that CoSeal was effective at sealing suture holes in PTFE vascular grafts. It is well known that sealing of PTFE grafts represent the greatest challenge due to leakage from holes created in the graft by needles used during suturing. There were no adverse events related to product use in this study, supporting the overall favorable benefit to risk ratio of CoSeal Surgical Sealant for use in sealing of vascular grafts.

2. European Multicenter Clinical Trial

An expanded, multicenter, non-randomized clinical trial was conducted in Europe to evaluate the safety and performance of CoSeal in sealing suture lines along synthetic and autologous vascular grafts in patients undergoing placement of vascular grafts using various types of graft materials. The multicenter trial included 131 patients treated in ten investigational centers in Germany and The Netherlands.

Table 12: Sites Achieving Sealing within 10 Minutes by Surgical Group	
	Success/Total (%)
Bypass Grafts	140/148 (96%)*
AV-Shunts	34/35 (96%)
Arteriotomies	18/18 (100%)
Total	192/201 (96%)*

*1 missing data

Table 13: Patients Achieving Sealing within 10 Minutes by Surgical Group	
	Success/Total (%)
Bypass Grafts	75/93 (81%)
AV-Shunts	25/27 (93%)
Arteriotomies	11/11 (100%)
Total	111/131 (85%)

Three different graft materials, PTFE, Dacron and autologous vein were used. The primary performance outcome was to achieve successful sealing within 10 minutes.

Table 14: Sites Achieving Sealing by Graft Material Group	
	Sealed with 10 Minutes Success/Total (%)
PTFE Grafts	97/106 (92%)
Dacron Grafts*	34/34 (100%)
Autologous Grafts	61/61 (100%)

*1 missing data

Table 15: Patients Achieving Sealing by Graft Material Group	
	Sealed with 10 Minutes Success/Total (%)
PTFE Grafts	48/65 (74%)
Dacron Grafts	19/20 (95%)
Autologous Grafts	44/46 (96%)

There were no significant adverse events related to product use reported in the European multi-center trial. The events reported were typical of patients with clinical conditions leading to vascular surgeries. One patient died during the study. The investigator indicated the myocardial infarction and death of this patient were "definitely not" sealant related.

This multicenter study demonstrated that CoSeal was effective at sealing suture holes in vascular grafts. There were no significant adverse events related to product use, supporting the overall favorable benefit to risk ratio of CoSeal for use in sealing of synthetic and autologous vascular grafts.

J. Conclusions Drawn from the Studies

The bench, animal and clinical testing provide a reasonable assurance that CoSeal Surgical Sealant is safe and effective when used in accordance with the labeling.

K. Panel Review

Two members of the Cardiovascular Devices Panel, a medical officer and a statistician, were asked to review this file. The panel members recommended that the labeling:

- include a precaution statement that in vivo testing demonstrated a mild skin sensitization response in and animal model, and similar testing in humans has not been conducted; and
- be reformatted such that the mixing instruction diagrams use color or symbols to more clearly distinguish between the two different polymer components.

L. CDRH Decision

CDRH concurred with the Panel reviewers' recommendations, and issued a letter to Cohesion Technologies, Inc., on October 5, 2001, advising that its PMA was approvable subject to the submission of final draft labeling as recommended by the Panel and the "General Conditions of Approval" for all PMA approved products as required by FDA. In an amendment received by FDA on October 9, 2001, Cohesion Technologies, Inc., submitted the required information.

FDA issued an approval order for the stated indication for the applicant's PMA, P010022, on _____.

The applicant's manufacturing facility was inspected and was found to be in compliance with the device Quality Systems Regulations on December 13, 2001.

M. Approval Specifications

Directions for Use: See Final Draft Labeling (Information for Use and Directions for Use)

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the Final Draft Labeling (Information for Use and Directions for Use).

Conditions of Approval: See Approval Order

Revised: 10/11/01: jlg, edh; 10/25/01: jlg, jzd; 11/1/01: jlg; 12/14/01: jlg, txn