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ETHICON
omnex
SURGICAL SEALANT

Add Ethicon™ logo
Add manufacturing symbol ETHICON, Inc.
Somerville, NJ 08876-0151

DESCRIPTION

ETHICON™ OMNEX™ Surgical Sealant is a synthetic tissue sealant consisting of a blend of two monomers, 2-octyl cyanoacrylate (2-OCA) and butyl lactoyl cyanoacylate (BLCA). The liquid formulation is contained in a crushable glass ampoule, which is housed in a single-use delivery device. The formulation is passed through a porous disc containing an initiator, mixed in a chamber, and delivered through a cannula. Following standard closure techniques using sutures, staples and/or clips, ETHICON™ OMNEX™ Surgical Sealant is applied to the anastomotic closure line. The polymerizing formulation is spread using the cannula such that it wets and intimately contacts the anastomotic closure. When polymerization is complete, a film is formed that mechanically interlocks the tissue and/or non-biological materials (i.e. synthetic graft sutures, staples, clips) and creates a flexible physical seal, independent of the body's clotting mechanism. The formation of this flexible physical seal prevents leakage of blood along the anastomotic closure line. ETHICON™ OMNEX™ Surgical Sealant begins to polymerize immediately on mixing with the initiator and forms a physical seal within 2 minutes after application. ETHICON™ OMNEX™ Surgical Sealant has been formulated to provide a strong physical seal that remains in place beyond the time required for natural healing, and eventually degrades via hydrolytic chain scission (over approximately 36 months), breaking down into smaller absorbable fragments.

The sterile, non-pyrogenic device is provided as a packaged single-use applicator and stored at room temperature.

INDICATIONS FOR USE

ETHICON™ OMNEX™ Surgical Sealant is indicated for use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage.

CONTRAINDICATIONS

- Do not use on patients with known hypersensitivity to cyanoacrylate or formaldehyde.
- Not for intravascular use.

WARNINGS

- ETHICON™ OMNEX™I Surgical Sealant s intended for use as an adjunctive sealant and is not to be used in place of sutures, staples, or mechanical closure.
- Biological fluids and other residual moisture must be removed from the entire circumference of the anastomosis prior to application and maintained moisture/fluid free for two (2) minutes post application. Proper clamping, clipping or ligation should be used to prevent blood seepage during application.
- Very small amounts of the product are required to create an effective seal. ETHICON™ OMNEX™ Surgical Sealant should be applied to the dry anastomotic closure lines by expressing a partial drop and evenly spreading into a thin film along the anastomotic closure line.
- ETHICON™ OMNEX™ Surgical Sealant is a fast setting sealant capable of adhering to body tissues and many other materials, such as latex gloves, and surgical instruments. Take necessary precautions to avoid contact with unintended surfaces.
- The cannula tip should not be cut or trimmed as this may expose the internal stainless steel wire which could then potentially damage the vessel. This stainless steel wire allows the user to bend the cannula and position it for sealant application in more difficult to reach areas.
- If ETHICON™ OMNEX™ Surgical Sealant is applied to a wet field, the non-adherent sealant will adhere to the fluid instead of the tissue. Remove the sealant with forceps or aspiration.

PRECAUTIONS

- Excessive pressure of the applicator's cannula tip against the vessel/graft edges or surrounding tissue can result in forcing the vessel/graft edges apart and potentially allowing sealant into the vessel. ETHICON™ OMNEX™ Surgical Sealant within the vessel could delay wound healing and/or result in local or embolic vascular obstruction.
- Avoid applying ETHICON™ OMNEX™ Surgical Sealant to anastomoses or suture lines when the lumen of the vessel is under negative pressure or suction to avoid unpolymerized product from being drawn into the vessel lumen. This concern is most relevant during cardiac procedures requiring closure and de-airing of the aorta.
- ETHICON™ OMNEX™ Surgical Sealant has not been clinically evaluated for use on coronary artery anastomoses or on the myocardium.
- The safety and performance of ETHICON™ OMNEX™ Surgical Sealant have not been demonstrated for use in pediatrics, children and pregnant women.
- Attempting to remove ETHICON™ OMNEX™ Surgical Sealant after it has polymerized on application sites, both intended and unintended sites, could result in tissue damage.
- The safety of ETHICON™ OMNEX™ Surgical Sealant has not been evaluated in patients receiving more than 4 units (1000 µl). 1000 µl of sealant is equivalent to four fully expressed units of ETHICON™ OMNEX™, Surgical Sealant (4 x 250 µl).
- Repeated use of ETHICON™ OMNEX™ Surgical Sealant in subsequent surgeries has not been studied.
- Although stabilizer components of the product have been classified as potential carcinogens, the quantities of these components in extracts of four units of polymerizing or polymerized sealants were below detection levels in a battery of genotoxicity tests.

- A 24-month chronic toxicity evaluation in a rat model has been completed. Results at various time points up to 24 months have indicated no adverse local reaction, systemic toxicity or evidence of carcinogenicity likely to be applicable to the product's use in humans. However, the product, which is designed to be degradable, did not degrade to any significant extent during the 24-month implantation period and as such the long-term safety effects of the degradation products have not been established.

CLINICAL STUDIES

Three clinical trials were conducted to support the safety and effectiveness of the ETHICON™ OMNEX™ Surgical Sealant. A feasibility study was conducted under IDE # G030143, and enrolled 10 patients at two (2) centers in the United States (US) and evaluated the safety and feasibility of sealing anastomotic suture lines with ETHICON™ OMNEX™ Surgical Sealant to provide hemostasis in patients undergoing arteriovenous shunt procedures receiving an expanded polytetrafluoroethylene (ePTFE) graft. The Multi-Center Pivotal Study enrolled 151 patients at 13 centers in the US and the European Union (EU) and evaluated the safety and effectiveness of ETHICON™ OMNEX™ Surgical Sealant for use as an anastomotic sealant to provide hemostasis in patients undergoing vascular reconstruction procedures receiving an ePTFE graft, as compared to a standard of care control. The Multi-Center Registry Study enrolled 105 patients at 5 centers in Germany, and evaluated the safety and effectiveness of sealing anastomotic suture lines with ETHICON™ OMNEX™ Surgical Sealant in patients undergoing vascular reconstruction procedures using various types of graft materials.

All of the trials used the final formulation of the ETHICON™ OMNEX™ Surgical Sealant. However, the delivery system was slightly different in each of the three trials, with the commercial design of the delivery system being used in the Multi-Center Registry Study. Non-clinical bench, biocompatibility, and animal testing demonstrated that ETHICON™ OMNEX™ Surgical Sealant delivered across various iterations of the delivery system design have comparable characteristics and performance. Although the feasibility and pivotal clinical data were collected on product with a slightly different delivery system design, the data support the approval of the ETHICON™ OMNEX™ Surgical Sealant with the commercial design of the delivery system. Summaries of these clinical trials are presented below.

Feasibility Study

A. Study Design

The study was a prospective, non-randomized, controlled, multi-center trial to evaluate the safety and feasibility of ETHICON™ OMNEX™ Surgical Sealant to seal anastomotic suture lines in patients undergoing arteriovenous (AV) shunt procedures receiving an ePTFE graft for dialysis. Ten (10) patients were enrolled at two (2) centers in the US. The objective of the study was to collect clinical data concerning the safety and feasibility of ETHICON™ OMNEX™ Surgical Sealant as an adjunctive anastomotic sealant to provide hemostasis.

Subjects underwent AV graft placement using standard surgical procedures (according to the Instructions for Use for the graft). After the graft was sutured in place, the vessel was clamped to prevent bleeding through the suture line, the graft and tissue surfaces were blotted dry, and small drops of ETHICON™ OMNEX™ Surgical Sealant were expressed from the delivery system and spread into a thin film along the anastomotic closure line.

B. Safety and Effectiveness Results

The clinical results show that the mean elapsed time from clamp release to observed hemostasis was 9.1 seconds (range 0 – 91 seconds). The percent of patients with immediate hemostasis was 90% (9/10). Immediate hemostasis was defined as zero (0) minutes from the time of clamp release to achieving hemostasis. Time to hemostasis was determined using a calibrated stopwatch provided to each study site for use in the study. The percent of patients achieving hemostasis at 1, 5, and 10 minutes were 90% (9/10), 100% (10/10), and 100% (10/10), respectively. No additional adjunctive measures, although allowed, were necessary to achieve hemostasis.

There was one possible device-related event during the course of the study. This adverse event was an occlusion of the graft and native vessel noted at the 12-week visit, an expected event for vascular access grafts that did not raise concerns for expansion to the pivotal study. No other device-related events were reported for the other nine patients in the study.

Multicenter Pivotal Study

A. Study Design

Patients were enrolled between April 26, 2004 and January 18, 2005. The database for this PMA reflected data collected through April 2005 and included 151 patients. There were 13 investigational sites, 10 in the United States and 3 in Europe.

The study was a prospective, randomized, controlled, open-label, multi-center trial conducted to evaluate the safety and effectiveness of ETHICON™ OMNEX™ Surgical Sealant (ETHICON™ OMNEX™) versus Control to seal anastomotic suture lines in patients undergoing vascular reconstruction procedures receiving an ePTFE graft. The 151 patients were

randomized 2:1, ETHICON™ OMNEX™ versus Control (a commercially available, adjunctive sealant comprised of oxidized regenerated cellulose, a legally marketed alternative with similar indications for use). Randomization was stratified based on the type of procedure, that is, whether the patient was undergoing a femoral bypass or vascular access procedure for dialysis. The objective of the study was to collect clinical data concerning the safety and effectiveness of ETHICON™ OMNEX™ for use as an anastomotic sealant to provide hemostasis and to show superiority to the control, which was considered the standard of care. The patients were evaluated during surgery, before discharge, and at 4 and 12 weeks follow-up.

Frequentist statistics were used to analyze the primary effectiveness endpoint, time to hemostasis from clamp release. For femoral bypass patients with more than one anastomotic site treated, the site with the longest time to hemostasis was used in the analysis. The primary effectiveness analysis was performed in two stages. The first stage was a test of non-inferiority, and the second a test of superiority, conditioning on the test for non-inferiority being significant. The statistical hypotheses for the first stage were as follows:

$$H_O: \mu_T - \mu_C = \delta$$

$$H_A: \mu_T - \mu_C < \delta,$$

where μ_T and μ_C are the population mean times to hemostasis for the ETHICON™ OMNEX™ and Control groups, respectively. The non-inferiority margin, δ, is 1 minute. Rejection of this null hypothesis ($p < 0.05$), in favor of the alternative, would provide evidence that ETHICON OMNEX is non-inferior to Control in its mean time to hemostasis. If, and only if, this null hypothesis is rejected ($p<0.05$), then the following statistical hypotheses was tested in the second stage:

$$H_O: \mu_T - \mu_C = 0$$

$$H_A: \mu_T - \mu_C \neq 0.$$

Rejection of this null hypothesis ($p < 0.05$) in favor of the ETHICON™ OMNEX™ treatment group would provide evidence of the superiority of ETHICON™ OMNEX™ over the Control in terms of mean time to hemostasis.

A minimum sample size of 100 ETHICON™ OMNEX™ and 50 Controls was necessary to provide 80% power ($p < 0.05$) to reject the non-inferiority null hypothesis. Moreover, this sample size also provided 80% power ($p < 0.05$) to reject the second stage superiority null hypothesis.

A secondary effectiveness analysis was performed to determine the proportion of subjects achieving immediate hemostasis or by 1, 5, or 10 minutes after clamp release. As with the primary effectiveness variable, femoral bypass patients with more than one anastomotic site treated had the site with the longest time to hemostasis used. These data were analyzed by the Cochran-Mantel-Haenszel procedure, stratified by the cross-classification of the study center and procedure. An additional effectiveness analysis was performed to ascertain the frequency of use of additional adjunctive measures to achieve hemostasis. Use of additional adjunctive agents was analyzed by the Cochran-Mantel-Haenszel procedure, stratified by the cross-classification of study center and procedure. Femoral bypass patients who required an additional agent for any anastomotic site were classified as having required use of the additional agent. In addition, safety was assessed by comparing adverse events and device-related adverse events through the 4-week and 12-week follow-up period. These analyses were not powered for sample size.

An independent medical monitor was used in this study to evaluate all safety- related events.

1. Clinical Inclusion and Exclusion Criteria

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

- Patients undergoing femoral bypass procedures or AV shunt procedures for hemodialysis access using ePTFE vascular grafts
- Prior written informed consent
- Age ≥ 18 years
- Patient agreement to return for follow-up evaluations.

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

- Patients with a known hypersensitivity for formaldehyde or cyanoacrylate
- Women with known pregnancy
- Current or recent (< 6 months) participation in another investigational study of surgical/therapeutic device, drug, or biologic
- Receiving anti-vitamin K anticoagulants within 4 days prior to surgery
- Receiving low molecular weight heparins within 4 days prior to surgery
- For femoral bypass procedures or AV shunt procedures, utilization of a gelatin or collagen coated graft material
- For femoral bypass procedures or AV shunt procedures, utilization of an autologous graft

2. Follow-up Schedule

All patients were scheduled for follow-up examinations at 48 hours, 4 weeks, and 12 weeks postoperatively.

Postoperatively, the objective parameters measured during the study included distal radial pulses (for AV shunt procedures), and both ankle and brachial pressure for determination of ankle-brachial index (for patients who had femoral bypass procedures). All patients also had standard clinical evaluations for adverse event assessments. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, endpoints included adverse events and device-related adverse events during the procedure hospitalization and from hospital discharge through the entire 12-week follow-up period.

With regards to effectiveness, the primary endpoint was the elapsed time from surgical clamp release to hemostasis, recorded in seconds. For femoral bypass patients with more than one anastomotic site treated, the site with the longest time to hemostasis was used in the analysis.

The secondary effectiveness endpoints were:

- Proportions of subjects achieving hemostasis at t = 0 (immediate) or by 1, 5, or 10 minutes of post clamp release
- Frequency of use of additional adjunctive measures to achieve hemostasis [e.g. additional applications of ETHICON™ OMNEX™ (treatment arm only) or other sealants (Control arm only), stitches, pledgets, administration of protamine, or other standard of care)

B. Accountability of PMA Cohort

At the time of database lock, 266 patients were screened with 151 enrolled in the study, 151 (100%) completed treatment, and 126 patients (83%) were available for analysis at the completion of the study, the 12 week post-operative visit.

Table 1. Patient Accountability

	ETHICON™ OMNEX™ % (n)	Control % (n)
Screened	266	
Randomized	100% (101)	100% (50)
Treated	100% (101)	100% (50)
Completed Surgery	100% (101)	100% (50)
Died in Hospital	2% (2)	0% (0)
Discharged	98% (99)	100% (50)
Completed 4 Week Follow-up	91% (92)	98% (49)
Completed Study (12 Week Follow-up)	80% (81)	90% (45)

C. Study Population Demographics and Baseline Parameters

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

Table 2. Patient Demographics by Age, Gender, and Surgical Procedure

	ETHICON™ OMNEX™ (n=101)	Control (n=50)
Age		
Mean ± SD	60.8 ± 14.3	61.4 ± 13.9
Median	62.0	61.0
Range	21 – 96	29 – 90
Gender		
Males: n (%)	66 (65.4%)	28 (56.0%)
Females: n (%)	35 (34.6%)	22 (44.0%)
Race		
Asian: n (%)	0 (0%)	0 (0%)
Black: n (%)	31 (30.7%)	14 (28%)
Hispanic: n (%)	7 (6.9%)	0 (0%)
White: n (%)	62 (61.4%)	36 (72%)
Other: n (%)	1 (1.0%)	0 (0%)
Procedure		
Femoral Bypass: n (%)	46 (45.5%)	23 (46.0%)
AV Access for Hemodialysis: n (%)	55 (54.5%)	27 (54.0%)

Gender Analysis:

In this study, women comprised 35% of the ETHICON™ OMNEX™ group versus 44% in the Control group. There was no significant difference in gender distribution between the ETHICON™ OMNEX™ and Control groups (P = 0.26). The gender distributions are consistent with the patient populations who have undergone femoral bypass and arteriovenous access for hemodialysis, compared to data available in the American College of Surgeons – National Surgical Quality Improvement Program (Marcus, RJ, Marcus, DA, Sureshkumar, KK, Hussain, SM, and McGill, RL. Gender differences in vascular access in hemodialysis patients in the United States: Developing strategies for improving access outcome. Gender Medicine, 4(3):193-204, 2007).

Treatment Sites per Patient:

Since ETHICON™ OMNEX™ or the Control material may have been used in more than one location in an individual patient, Table 6 below shows the number of sites treated/patient in this study. However, the effectiveness results were based on per-patient statistics.

Table 3. Treatment Sites per Patient

	ETHICON™ OMNEX™	Control
Total Number of Patients Treated:	101	50
Number of Patients with 1 Site Treated:	57	27
Number of Patients with 2 Sites Treated:	40	21
Number of Patients with 3 Sites Treated:	4	2
Total Number of Sites Treated:	149	75

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the total cohort of 151 patients and the 126 patients that completed the 12 week follow-up period. As a key safety outcome, there were no unanticipated adverse device effects (UADE) in this investigation.

Adverse effects that occurred in the PMA clinical study:
The adverse events in this study are presented below in Tables 4 and 5. Table 4 provides a summary of vascular and bleeding complication adverse events reported for the ETHICON™ OMNEX™ treated and Control treated patients.

Table 4: Vascular or Bleeding Complications Adverse Events

	ETHICON™ OMNEX™ (n=101) % (n)	Control (n=50) % (n)
Number of Patients with at Least 1 Vascular or Bleeding Complication	22.8% (23)	40% (20)
Bleeding Complications		
Bleeding, procedure	2% (2)	0% (0)
Bleeding, post procedure	2% (2)	2% (1)
Hematoma	2% (2)	12% (6)
Coagulopathy	1% (1)	0% (0)
Vascular Complications		
Occlusion of Graft/Vessel	11.9% (12)	16% (8)
Edema	5% (5)	8% (4)
Thrombosis	5% (5)	6% (3)

Results show that the number of patients with at least one vascular or bleeding complication was greater in the control than ETHICON™ OMNEX™, and the difference was statistically significant, although the study was not powered for this analysis ($p < 0.035$).

In addition, the results are similar between the two treatment groups and are representative of events expected from patients undergoing vascular surgery for vascular access or occlusive vascular disease with the exception of hematoma (control 12% and ETHICON™ OMNEX™ 2%; $p < 0.016$), although the study was not powered for this analysis.

Table 5 shows all other adverse events reported by three or more patients treated with ETHICON™ OMNEX™ or control.

Table 5: Other Adverse Event[1] Complications Reported by Three or More Patients Treated

	ETHICON™ OMNEX™ (n=101) % (n)	Control (n=50) % (n)
Infection[2]	9.9% (10)	16% (8)
Pain	8.9% (9)	10% (5)
Erythema	8.9% (9)	2% (1)
Wound Infection[3]	7.9% (8)	4% (2)
Dehiscence	5% (5)	0% (0)
Renal Failure	4% (4)	4% (2)
Lymphocele/Lymph Fistula	3% (3)	0% (0)

[1] All adverse events other than vascular or bleeding complications reported
[2] Infection was defined as non-wound infections reported
[3] Wound infection was defined as surgical incision site infections reported

2. Effectiveness Results

Primary Endpoint

The primary effectiveness outcome parameter measured was time to hemostasis for patients treated with ETHICON™ OMNEX™ to that of patients treated with the Control. For femoral bypass patients with more than one anastomotic site treated, the site with the longest time to hemostasis was used in the analysis. These results are presented in Table 6.

Table 6. Time to Hemostasis (sec)[1] Summary – All Patients

	ETHICON™ OMNEX™ (n=101)	Control (n=50)
Mean Time to Hemostasis [2,3]	119.3	403.8

[1] The anastomotic site with the longest time to hemostasis was used for femoral bypass patients with multiple sites treated. All times > 10 minutes were replaced by 10 minutes.
[2] Adjusted for study center and type of procedure
[3] Test of hypothesis that ETHICON™ OMNEX™ mean is no more than one minute longer than that of the control; test of non-inferiority p-value is < 0.001; Test of superiority p-value is < 0.001.

Multiple analyses were conducted to evaluate the effectiveness data by procedural type and by patient. These analyses demonstrated that all study objectives were met. The results of the study showed that patients who received ETHICON™ OMNEX™ had a statistically significant faster time to hemostasis than that of the control ($p < 0.001$).

Secondary Endpoints

The secondary effectiveness endpoints were:

- Number of patients who achieved hemostasis within 0 (immediate), 1, 5, and 10 minutes
- Number of patients who required additional adjunctive agents in order to achieve hemostasis

Table 7. Time to Hemostasis[1] by Minute Intervals for All Procedures - All Patients

Interval	ETHICON™ OMNEX™ (n=101) % (n)	Control (n=50) % (n)
0 (immediate)	54.5% (55)	10% (5)
0 - 1 minute	60.4% (61)	14% (7)
0 - 5 minutes	88.1% (89)	32% (16)
0 - 10 minutes	93.1% (94)	58% (29)
> 10 minutes	6.9% (7)	42% (21)

[1] The anastomotic site with the longest time to hemostasis was used for femoral bypass patients with multiple sites treated. All times > 10 minutes were replaced by 10 minutes

As with the primary variable, femoral bypass patients with more than one anastomotic site treated had the site with the longest time to hemostasis used. These data were analyzed by the Cochran-Mantel-Haenszel procedure, stratified by the cross-classification of the study center and procedure.

Table 8. Use of Additional Adjunctive Agents to Achieve Hemostasis – All Patients

	ETHICON™ OMNEX™ (n=101) % (n)	Control (n=50) % (n)
At least one additional agent required[1]	30.7% (31)	44 % (22)
One additional unit of assigned treatment	10.9% (11)	30% (15)
Stitches	6.9% (7)	14% (7)
Pledgets	0% (0)	0% (0)
Protamine	6.9% (7)	16% (8)
Other	11.9% (12)	6% (3)

[1] Total number of individual agents may exceed the number of patients who had at least one agent used because patients may have had multiple agents used and because multiple anastomotic sites were treated in femoral bypass patients

Use of additional adjunctive agents was analyzed by the Cochran-Mantel-Haenszel procedure, stratified by the cross-classification of study center and procedure. Femoral bypass patients who required an additional agent for any anastomotic site were classified as having required use of the additional agent. A greater proportion of patients in the control group (44.0%) required at least one additional agent than patients in the ETHICON OMNEX group (31%), although the difference did not achieve statistical significance ($p = 0.08$).

During the clinical investigation, the number of ETHICON™ OMNEX™ units used per patient to effectively seal a typical vessel was an average of 1.7 ± 0.88 units (range 1 - 4 units), and for Control, using oxidized regenerated cellulose, 2.2 ± 1.04 units (range 1 - 4 units). The number of ETHICON™ OMNEX™ units used per anastomosis to effectively seal a typical vessel was an average of 1.1 ± 0.25 units (range 1 - 2 units), and for Control, 1.5 ± 0.48 units (range 1 - 2) and is detailed in Table 9 below.

Table 9. Amount of Sealant used in the Clinical Pivotal Study per Patient and by Procedure

	ETHICON™ OMNEX™		Control	
	Patient	Procedure	Patient	Procedure
Mean Units Used	1.7	1.1	2.2	1.5
Std Dev	0.88	0.25	1.04	0.48
Range	1 – 4	1 - 2	1 - 4	0.5 - 2

3. Subgroup Analysis

Inclusion and exclusion criteria were chosen to avoid gender bias. The results of the Pivotal trial demonstrated that there were no significant differences in the Primary Objective (average time to hemostasis) due to gender, with mean results of 107 sec for females and 126 sec for males. In the Control group, the average time to hemostasis was 389 sec for females and 415 sec for males. There were no significant differences in the occurrence of adverse events between males (67%) and females (71%) in the ETHICON™ OMNEX™ treatment group with none in either group directly attributable to ETHICON™ OMNEX™. In the Control group, adverse event occurrence was 71% in males and 68% in females. No important differences in success rate or adverse event rate were detected between males and females in this patient population, and the results presented are representative of both genders.

European Multi-Center Registry Study

A. Study Design

A prospective, non-randomized, single-arm, multi-center trial was conducted in Germany to evaluate the safety and effectiveness of ETHICON™ OMNEX™ to seal anastomotic suture lines in patients undergoing multiple types of vascular reconstruction procedures using various types of graft materials. One hundred five patients (105) were enrolled at five (5) study centers.

B. Safety and Effectiveness Results

1. Safety Results

There were no significant adverse events related to the product use reported in the Single Arm European Study. The events reported were typical of patients with clinical conditions related to vascular surgeries without the use of ETHICON™ OMNEX™.

2. Effectiveness Results

The primary effectiveness endpoint was time to hemostasis. Overall, immediate hemostasis (at time 0) was achieved in 71% of the 158 application sites from 105 treated patients. Hemostasis was achieved in 94% of

application sites within one minute; in the remaining 6% of application sites, hemostasis was achieved within eight minutes. Overall, mean time to hemostasis by anastomotic site was 23.2 seconds with a 95% confidence interval of 11.0 to 35.3 seconds.

Table 10. Time to Hemostasis

		AV Access Procedure	Bypass & Abdominal Aortic Aneurysm (AAA)	Endar-terectomy & Patch	Total
By Patient	# of Patients	7	75	23	105
	Mean (sec)	4.6 ± 8.5	39.6 ± 104.6	23.1 ± 55.9	33.7 ± 92.5
	Median (sec)	0.0	0.0	5.0	0.0
	Range (sec)	0 – 22	0 – 480	0 – 266	0 - 480
By Anastomoses	# of Anastomotic Sites	10	124[1]	24	158
	Mean (sec)	3.2 ± 7.3	25.0 ± 83.7	22.1 ± 54.9	23.2 ± 77.2
	Median (sec)	0.0	0.0	2.5	0.0
	Range (sec)	0 – 22	0 – 480	0 – 266	0 - 480

[1] Time to hemostasis was not captured at one anastomotic site.

Secondary effectiveness variables included the number of anastomotic sites receiving each type of graft material and the number of patients who achieved hemostasis within 0 (immediate), 1, 5, and 10 minutes.

Table 11. Graft Material Used

Graft Material	AV Access Procedure % (n)	Bypass & AAA % (n)	Endarterectomy & Patch % (n)	Total[1] % (n)
PTFE	20% (2)	41.1% (51)	4.2% (1)	34.2% (54)
Dacron	0% (0)	25% (31)	75% (18)	31% (49)
Autologous	70% (7)	33.9% (42)	16.7% (4)	33.5% (53)
Other	10% (1)	0% (0)	4.2% (1)	1.3% (2)

[1] Number of anastomotic sites treated

Table 12. Time to Hemostasis by Graft Type

Graft Type	# of Anastomotic Sites	Time Interval			
		0 (immediate)	0 –1 minute	0-5 minutes	0-10 minutes
PTFE	54	64.8% (35)	85.2% (46)	90.7% (49)	100% (54)
Dacron[1]	48	66.7% (32)	97.9% (47)	100% (48)	100% (48)
Autologous	53	81.1% (43)	98.1% (52)	100% (53)	100% (53)
Other	2	100% (2)	100% (2)	100% (2)	100% (2)

[1] Time to hemostasis was not captured at one anastomotic site in this group

During the clinical investigation, the number of ETHICON™ OMNEX™ units used per patient to effectively seal a typical vessel was an average of 1.56 ± 0.62 units (range 1 - 4 units). For femoral bypass and open AAA repair procedures, the number of ETHICON OMNEX units used per anastomosis to effectively seal a typical vessel was an average of 1.02 ± 0.15 units (range 1 - 2 units). For endarterectomy and patch procedures, the number of ETHICON™ OMNEX™ units used per anastomosis to effectively seal a typical vessel was an average of 1.09 ± 0.29 units (range 1-2 units). For AV access procedures, the number of ETHICON™ OMNEX™ units used per anastomosis to effectively seal a typical vessel was an average of 1.43 ± 0.53 units (range 1 - 2 units), as depicted in Table 13 below.

Table 13. Amount of Sealant used in the European Multi-Center Registry Study per Patient and by Procedure

	ETHICON™ OMNEX™	
	Patient	Procedure
Mean Units Used	1.56	1.02
Std Dev	0.62	.15
Range	1 - 4	1 - 2

3. Subgroup Analysis

In the European Registry Study where there was no control group (single-arm), women comprised 24% of the study when all the procedures in the study were combined. No statistical analysis was performed to determine if this ratio is consistent with the general patient population undergoing the same procedures.

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.

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

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

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

For the specific adverse events that occurred in the clinical studies, please see the Clinical Studies section above.

DIRECTIONS FOR USE

Prior to application of ETHICON™ OMNEX™ Surgical Sealant , the vessel segment that is being treated should be clamped and depressurized. The anastomotic site should be mechanically closed with sutures or staples.

APPLICATOR PREPARATION:

1. Remove the ETHICON™ OMNEX™ Surgical Sealant applicator from the sterile pouch and hold the applicator with the cannula tip pointing downward.
2. Apply pressure to the applicator lever to crush the inner glass ampoule. Then, release pressure on the applicator lever.
3. Squeeze the applicator lever again allowing the liquid to completely express into the cannula cover (i.e. mixing chamber). Avoid creating excessive foam or bubbles by expressing the liquid slowly into the mixing chamber. Then, release pressure on the applicator allowing the liquid to draw back into the applicator unit. **Repeat this mixing step two (2) additional times. Thorough mixing is essential for optimal performance.** The liquid should fill approximately one-third of the cannula cover.
4. Remove and discard the cannula cover. The applicator is now ready for use once the target surgical field has been prepared for application.

SITE PREPARATION AND APPLICATION:

1. Prepare the anastomotic site to be treated by patting dry with dry, sterile gauze or a sterile sponge. For proper adherence, ETHICON™ OMNEX™ Surgical Sealant must have direct contact with the tissue or graft material.
2. **Very small amounts of sealant are required to create an effective seal.** Apply ETHICON™ OMNEX™ Surgical Sealant to the **dry anastomotic closure line of the clamped/depressurized vessel.** Squeeze partial drops and spread with the applicator tip on the anastomotic surface to create a thin film.
3. Ensure complete application over the anastomotic closure lines including all suture bites, needle holes, staple holes, and clip holes. ETHICON™ OMNEX™ Surgical Sealant forms a flexible polymeric seal at the tissue surface when completely set.
4. Allow two minutes (120 seconds) to pass before removing clamps to assure complete polymerization of ETHICON™ OMNEX™. Surgical Sealant. Verify that ETHICON™ OMNEX™ Surgical Sealant has set by gently touching the seal with the tip of the applicator. Full polymerization is confirmed when the thin film of sealant is no longer tacky.
5. Inspect and verify that the seal is effective. In the event excessive bleeding is observed after clamp removal, re-clamp, pat dry and reapply ETHICON™ OMNEX™ Surgical Sealant as previously indicated, or use other adjunctive therapies. If ETHICON™ OMNEX™ Surgical Sealant is applied to a wet field, the non-adherent sealant will adhere to the fluid instead of the tissue. Remove the sealant with forceps or aspiration.

HOW SUPPLIED:

- ETHICON™ OMNEX™ Surgical Sealant is packaged and supplied as a Sterile Single Use Only Device;
- ETHICON™ OMNEX™ Surgical Sealant unit maximally dispenses approximately 250 µL of sealant;
- Product can be disposed through normal hospital practice.

STORAGE:

Store at controlled room temperature between 20° to 25° C (68° to 77° F); temporary excursions permitted to 15° or up to 30° C (59° to 86° F). Do not use ETHICON™ OMNEX™ Surgical Sealant after expiration date.

STERILITY:

STERILE SINGLE USE ONLY

ETHICON™ OMNEX™ Surgical Sealant is originally sterilized by dry heat and ethylene oxide gas. Do not resterilize. Do not use if the package is opened or damaged. Discard any unused material following completion of the medical procedure.

REPORTING:

Physicians should use the following toll free number 1-877-ETHICON (valid in the USA only), when reporting adverse reactions or potentially threatening complications involving ETHICON™ OMNEX™. Surgical Sealant.

PATIENT COUNSELING INFORMATION:

Prior to surgery, at the time of surgical consent, patients should be asked if they have any known hypersensitivity to cyanoacrylates or formaldehyde. Patients should be counseled that the long-term safety effects of the degradation products have not been established. A patient card (located within the device packaging) should be provided to all patients implanted with ETHICON™ OMNEX™ Surgical Sealant.

CAUTION:

Federal (USA) Law restricts this device to sale by or on the order of a healthcare practitioner.

add symbol chart - reference OMNEX PM72363C – Need Rx symbol to be added, do not need EC REP, CE mark
add code PM72403A
add STATUS: 04/2010