

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Polymerizing Sealant
Device Trade Name:	Ethicon™ OMNEX™ Surgical Sealant
Applicant Name and Address:	Ethicon, Inc. (Raleigh) 5250 Greens Dairy Road Raleigh, NC 27616 United States of America
Date(s) of Panel Recommendation:	None
PMA Application Number:	P060029
Date of FDA Notice of Approval:	June 3, 2010
Expedited:	Not applicable

II. INDICATIONS FOR USE

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

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

Ethicon™ OMNEX™ Surgical Sealant (Ethicon™ OMNEX™) is a synthetic tissue sealant consisting of a blend of two monomers, 2-octyl cyanoacrylate (2-OCA) and butyl lactoyl cyanoacrylate (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™ 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™ begins to polymerize immediately on mixing with the initiator and forms a physical seal within 2 minutes after application. Ethicon™ OMNEX™ 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 device is provided as a packaged single-use applicator and stored at room temperature.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the control of bleeding, including use of direct pressure, sutures, staples, and/or electrocautery. In addition, absorbable hemostatic agents such as bovine/porcine gelatin powder and sponges, and hemostats made from collagen as well as oxidized cellulose are commercially available and are used for stopping bleeding. Synthetic liquid polymer sealants, such as those consisting of hydrogel or bovine albumin/gluteraldehyde, are also available to control bleeding in cardiac and vascular surgery. Each alternative has its own advantages and disadvantages.

VII. MARKETING HISTORY

Ethicon™ OMNEX™ Surgical Sealant has regulatory approval for commercial distribution starting in 2006 and has been sold in the following countries/regions: European Union, Russia, Czech Republic, Australia, Brazil, Mexico, Argentina, Chile, Uruguay, Columbia, Venezuela, Peru, South Africa, Israel, and Lebanon. Ethicon™ OMNEX™ Surgical Sealant has not been withdrawn from marketing for any reason relating to the safety or effectiveness of the device.

VIII. 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 Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

In Vitro Testing

In vitro (bench) testing was conducted to characterize sterilized Ethicon™ OMNEX™ Surgical Sealant and to ensure that the same product is being manufactured on a lot-to-lot basis. The findings from the *in vitro* testing are

summarized in Table 1. As illustrated in the table, all results support the safety and effectiveness of the product.

Table 1. Summary of *In Vitro* Testing and Results

In Vitro Test:	Test Article:	Results:
Viscosity Determination	Final Formulation: Ethicon™ OMNEX™	Acceptable internal resistance to flow
Average Setting Time	Final Formulation: Ethicon™ OMNEX™	Sufficient polymerization to adequately seal the suture line within an average of < 15 seconds
Working Time	Final Formulation: Ethicon™ OMNEX™	Time available to surgeon to use sealant before it polymerizes within the applicator is > 120 seconds
Identity	Final Formulation: Ethicon™ OMNEX™	All lots tested matched reference identity chromatogram
Molecular Weight and Polydispersity Index Analysis	Final Formulation: Ethicon™ OMNEX™	Molecular weight range and polydispersity index (PDI) demonstrate consistency of product across lots
Delivery System Performance	Final Formulation: Ethicon™ OMNEX™	Product consistently delivers between 220 µl to 235 µl of sealant per device
Degradation Study	Final Formulation: Ethicon™ OMNEX™	In saline at 50°C, complete degradation is estimated to be between 2.1 and 2.5 yrs

Sterilization

Ethicon™ OMNEX™ Surgical Sealant is dry heat sterilized after packaging into glass ampoules, and then terminally sterilized with Ethylene Oxide in compliance with ANSI/AAMI/ISO ST63:2002, ANSI/AAMI/ISO 11135, ANSI/AAMI/ISO 10993-7, and ANSI/AAMI/ISO TIR 19:1998. Based on the design, manufacturing, and the validated sterilization procedure for Ethicon™ OMNEX™ Surgical Sealant, the test results indicate that the device will maintain a Sterility Assurance Level (SAL) of 10⁻⁶ when sterilized according to the validated procedures.

Packaging and Shelf Life

Ethicon™ OMNEX™ Surgical Sealant is packaged in a delivery system that contains a single ampoule sealing the monomers and stabilizers until ready for use. The product is sealed within a Tyvek® pouch, with 4 pouches per box. Qualification testing was performed for packaging design performance, packaging shelf-life, and device shelf-life for the Ethicon™ OMNEX™ Surgical Sealant. A 12-month shelf-life has been established for the product.

Biocompatibility

Biocompatibility of Ethicon™ OMNEX™ Surgical Sealant was evaluated in accordance with ISO 10993-1, Biological Evaluation of the Medical Devices – Part 1: Evaluation and Testing and FDA Blue Book Memorandum G95-1. All testing was conducted at Toxikon, Inc. in accordance with FDA good laboratory practice (GLP) regulations (21 CFR, Part 58).

Tests conducted on Ethicon™ OMNEX™ Surgical Sealant were appropriate for an implant device that is in permanent contact with tissue (> 30 days). The findings from the biocompatibility testing are summarized in Table 2. All test results indicated that the materials and processes used to manufacture Ethicon™ OMNEX™ Surgical Sealant and delivery system are biocompatible and suitable for their intended use.

Table 2. Summary of Biocompatibility Testing and Results

Biocompatibility Test:	Test Article:	Results:
Cytotoxicity	Final Formulation: Ethicon™ OMNEX™; • Polymerized film in MEM +10% FBS	Non-cytotoxic
Intracutaneous Reactivity	Final Formulation: Ethicon™ OMNEX™; • Unpolymerized sealant* in saline • Polymerized film in sesame oil	Non-irritating
Dermal Sensitization	Final Formulation: Ethicon™ OMNEX™; • Unpolymerized sealant* in saline • Polymerized film in sesame oil	Not a sensitizer
Acute Toxicity	Final Formulation: Ethicon™ OMNEX™; • Unpolymerized sealant* in saline • Polymerized film in sesame oil	Not an acute toxin
Pyrogenicity	Final Formulation: Ethicon™ OMNEX™; • Unpolymerized sealant* in saline	Non-pyrogenic
Hemolysis	Final Formulation: Ethicon™ OMNEX™; • Unpolymerized sealant* in saline	Non-hemolytic
Ames Assay	Final Formulation: Ethicon™ OMNEX™; • Unpolymerized sealant* in saline • Polymerized film in sesame oil	Non-mutagenic in bacteria
Mouse Lymphoma	Final Formulation: Ethicon™ OMNEX™; • Polymerized film in Fisher's +5%HS	Non-mutagenic in mammalian cells
<i>In Vitro</i> Chromosomal	Final Formulation: Ethicon™	Non-clastogenic <i>in</i>

Biocompatibility Test:	Test Article:	Results:
Aberration	OMNEX™: • Polymerized film in Ham's F12	<i>vitro</i>
<i>In Vivo</i> Mouse Micronucleus	Final Formulation: Ethicon™ OMNEX™: • Unpolymerized sealant* in saline • Polymerized film in sesame oil	Non-clastogenic <i>in vivo</i>
Cytotoxicity	Final Formulation: Ethicon™ OMNEX™: • Polymerized film in MEM +10%FBS	Non-cytotoxic
Intracutaneous Reactivity	Final Formulation: Ethicon™ OMNEX™: • Unpolymerized sealant* in saline • Polymerized film in sesame oil	Non-irritating

*sealant polymerized during the conduct of the test

Because this product is applied on the outside of the vessel and is not intended for direct contact with blood, FDA generally does not request full hemocompatibility testing. However, reports from plasma recalcification time and complement activation testing were provided for this device, with no adverse findings.

For all tests conducted using non-saline extracts (e.g., tissue culture media, oil), extractions were conducted using fully polymerized product. These extractions do not allow for assessment of the toxicity of starting or intermediate compounds. In addition, none of the biocompatibility screening tests are designed to investigate the toxicity of the final breakdown products. Therefore, results from a variety of animal implant studies (Table 3), as well as results from a literature review, were used to address the toxicity of the starting, intermediate, and final breakdown products of this device. The literature review was based on the amount of chemicals present in 1000 µl of sealant, which is equivalent to four fully expressed units of Ethicon™ OMNEX™ Surgical Sealant (4 x 250 µl). 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.

Results from the animal implant studies, and data from the literature review, were used to justify omission of conventional muscle implant, sub-chronic toxicity, chronic toxicity and carcinogenicity biocompatibility screening studies. Instead, several animal implant studies were conducted, including a 24-month high dose (*in situ* polymerization) implant study in rats. Results from these animal studies are provided in Table 3 below.

B. Animal Studies

Ethicon™ OMNEX™ Surgical Sealant was subjected to a series of acute and chronic animal studies. The intent of the studies was to demonstrate safety of the device by acceptable functional performance of the subject devices in an *in vivo* setting. Additionally, the studies were intended to ensure that the devices do not cause adverse biological responses.

Ethicon, Inc. has conducted five (5) preclinical studies that evaluated the safety of the Ethicon™ OMNEX™ Surgical Sealant. These studies were conducted in accordance with Good Laboratory Practices (GLP) per 21 CFR§ 58. All product was implanted successfully, and all animals survived to the pre-determined study endpoints. Table 3 outlines the animal studies performed and the relevant findings for each study.

Table 3. Summary of Animal Studies Performed

Study Type:	Test Articles:	Number of Animals and Amount of Product Tested:	Follow-Up Duration:	Relevant Findings:
Ovine Graft Study (Iliac anastomosis)	Test Article: Final Formulation - Ethicon™ OMNEX™ Control: Oxidized regenerated cellulose	8 Ethicon™ OMNEX™ and 8 Control sites in 12 animals. Dose: As required to seal anastomosis	Intervals up to 18 month	Moderate to marked chronic active reaction at 2 and 4 weeks, decreasing to a mild reaction at 6 and 18 months. The investigators concluded that use of the surgical sealant is effective and does not result in any adverse complications of vessel patency, vessel stenosis, and degree of tissue reactivity.
Ovine Venotomy Study	Test article: Final Formulation - Ethicon™ OMNEX™ Control: Competitor	16 animals: 8 Ethicon™ OMNEX™ and 16 Controls (2 groups). Dose: As	1 month	Minimal to moderate pyogranulomatous inflammation. Due to the 1 month duration of the study,

Study Type:	Test Articles:	Number of Animals and Amount of Product Tested:	Follow-Up Duration:	Relevant Findings:
	products	required to seal anastomosis		resolution of inflammation was not observed, as was found in the longer term studies.
Rodent Sciatic Nerve Study	Test article: Final Formulation - Ethicon™ OMNEX™ Control: saline	20 rats: 10 Ethicon™ OMNEX™ and 10 Controls. Dose: ≈ 10 µl	2 week	Mild tissue reaction. Due to the 2 week duration of the study, resolution of inflammation was not observed, as was found in the longer term studies.
Rodent Intraperitoneal Implantation	Test article: Final Formulation - Ethicon™ OMNEX™	20 rats: 20 Ethicon™ OMNEX™ no controls. Dose: 4 x 10 µl/rat	Intervals up to 23 month	Mild to marked macrophage response. Based on the change in sealant mass and morphological changes observed in this study and under the specified conditions, the estimated mass loss at 23 months is 75% of the initial mass. This predicts at least 90% mass loss in a time range of 30 to 36 months, considering that the degradation profile remains constant.
Rodent Subcutaneous Implantation	Test article: Ethicon™ OMNEX™	560 rats: 280 Ethicon™ OMNEX™	24 month	Minimal to mild chronic granulomatous

Study Type:	Test Articles:	Number of Animals and Amount of Product Tested:	Follow-Up Duration:	Relevant Findings:
	Control: saline	and 280 Control studied at various time points to 2 years. Dose: 2 x 100 µl/rat		inflammation/ fibrosis. A low but increased incidence of well- known rodent- specific fibrosarcomas not relevant for humans. Ethicon™ OMNEX™ present throughout study. 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.

X. SUMMARY OF PRIMARY 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:

$$H_0: \mu_T - \mu_C = \delta$$

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

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:

$$H_0: \mu_T - \mu_C = 0$$

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

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 \geq 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 4. 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 5 depicts the patient demographics.

Table 5. 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%)

	Ethicon™ OMNEX™ (n=101)	Control (n=50)
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 6. 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 7 and 8. Table 7 provides a summary of vascular and bleeding complication adverse events reported for the Ethicon™ OMNEX™ treated and Control treated patients.

Table 7: 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 8 shows all other adverse events reported by three or more patients treated with Ethicon™ OMNEX™ or control.

Table 8: Other Adverse Event¹ 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 9.

Table 9. 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 10. Time to Hemostasis¹ 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 11. 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 12 below.

Table 12. 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 13. Time to Hemostasis

		AV Access Procedure	Bypass & Abdominal Aortic Aneurysm (AAA)	Endarterectomy & 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 14. 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 15. 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 16 below.

Table 16. 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.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety and Effectiveness Conclusions

The non-clinical studies indicate that the Ethicon™ OMNEX™ Surgical Sealant meets or exceeds safety and performance specifications. Multi-center clinical trials have demonstrated that Ethicon™ OMNEX™ is safe and effective for its intended use as a treatment in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage. These clinical trials investigated use with various graft types (e.g. ePTFE, Dacron, autologous graft) and in various types of procedures (e.g. femoral bypass, arteriovenous access, AAA repair, endarterectomy) which did not impact the safety or effectiveness of the product. 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. Pre-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. Results from non-clinical and clinical evaluations provide valid scientific evidence and reasonable assurance that the device is safe and effective. Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

XIII. CDRH DECISION

CDRH issued an approval order on June 3, 2010. The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

Revised: jlg 5/11/2010

Revised: jlg 5/13/2010 (Paul & Ken on AE info and gender citation)

Revised: kjc 5/13/2010

Revised: jlg 5/25/2010