

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I GENERAL INFORMATION

Classification Name:	Not yet classified.
Device Generic Name:	Intraoperative Gel
Device Trade Name:	Oxiplex®
Applicant's Name and Address:	FzioMed, Inc. 231 Bonetti Drive San Luis Obispo, California 93401
Date(s) of Panel Recommendation:	(To be determined.)
Premarket Approval Application (PMA) Number:	P070023
Date of Notice of Approval to Applicant:	(To be determined.)

II INDICATIONS FOR USE

Oxiplex is indicated for use as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain and neurological symptoms.

III CONTRAINDICATIONS

Oxiplex is contraindicated for use in the presence of frank infection.

IV WARNINGS AND PRECAUTIONS

- Oxiplex must be used according to the instructions for use.
- Oxiplex is supplied sterile for single use only. Do not re-sterilize.
- Do not use if packaging or seal has been damaged or opened. Discard any opened and unused product.
- Oxiplex is not a dural sealant. Repair dural defects prior to use.
- Oxiplex has not been evaluated in the presence of a malignancy in the spine.
- The use of Oxiplex in pregnant women, nursing mothers or children has not been evaluated.
- The use of Oxiplex in combination with other medical devices has not been evaluated.
- Any hemostatic agent used during the surgical procedure should be removed from the surgical site prior to application of Oxiplex. The use of Oxiplex in combination with hemostatic agents has not been evaluated.
- Although there were no reports of foreign body reactions during the clinical investigation of Oxiplex, foreign body reaction may occur as with any surgical adjuvant.

V DEVICE DESCRIPTION

Oxiplex is an absorbable, clear, viscoelastic gel that is comprised of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in sterile water for injection. Calcium chloride (CaCl₂) is added for stability and sodium chloride (NaCl) is

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added for isotonicity. Oxiplex is non-pyrogenic and contains no animal or bacterial components. No color additives are used in the device.

Oxiplex is provided sterile in a 3 mL syringe, together with a sterile, flexible applicator for application during surgery. These components are packaged together in a thermoform tray, sealed with a Tyvek® lid, and terminally sterilized by steam. Oxiplex is for single use only.

Oxiplex is applied during lumbar spine surgery. Following the primary surgical procedure, after hemostasis is achieved and immediately prior to wound closure, Oxiplex is applied to the operative site surrounding the dura and the nerve root and coating the neural tissue. Oxiplex is easily placed around exposed tissues (e.g., nerve root and dura) to fill the surgical site to the ventral surface of the vertebral lamina and coat the neural tissues. After application, the surgical procedure is concluded according to the surgeon's standard technique. The device remains at the site of application for a period of time, providing a protective environment and physical separation of tissues during the healing process. Oxiplex is cleared by the body (excreted, not metabolized) and does not require a second operation for removal.

As shown in this Pivotal Study, Oxiplex is intended to coat and protect neural tissues and thereby significantly reduce nerve root-related postoperative pain and related symptoms following lumbar disc surgery.

Preclinical studies have demonstrated that Oxiplex is biocompatible, non-inflammatory, and does not inhibit normal healing of neural tissues, dura or bone.

The device was CE marked in the European Union in 2001 and was first marketed outside the U.S. in 2002. Oxiplex is now approved in 49 countries, including Canada and Australia. Over 100,000 units have been commercially distributed to date.

VI ALTERNATIVE PRACTICES AND PROCEDURES

There is no alternative device approved by the Food and Drug Administration (FDA) for application during lumbar surgery for the reduction of pain and symptoms.

VII MARKETING HISTORY

Oxiplex was first marketed outside the U.S. in 2002 and is currently approved in 49 countries. Over 100,000 units have been commercially distributed to date. Oxiplex has not been withdrawn from sale in any country for any reason related to safety and effectiveness of the device.

VIII POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

1. In U.S. Feasibility and Pivotal Studies, there were no significant differences in the number of subjects having adverse events (AEs) or serious adverse events (SAEs) between the Oxiplex (surgery plus Oxiplex) and Control (surgery only) groups.
2. There were no AEs leading to discontinuation of any subject from either the Feasibility or the Pivotal Studies or discontinuation of the Feasibility or Pivotal Studies.
3. One (1) reoperation occurred in the Oxiplex group, while six (6) reoperations occurred in the Control group (P=0.0665).

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4. There were no significant differences between the Oxiplex group and the Control group with respect to any of the following variables: hematology; chemistry; urinalysis; physical examination; postoperative neurology examination; and vital signs. There was good balance between concomitant therapies received by the Oxiplex group and the Control group.

IX SUMMARY OF PRECLINICAL STUDIES

Chemical and Physical Characterization

Oxiplex components were verified through testing and/or manufacturer’s certification to meet USP requirements. Each lot of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) was verified for identity using Fourier Transform Infra Red (FTIR) analysis.

In addition to chemical characterization of the product components, ethylene oxide, aldehyde and endotoxin testing and physical characterization of Oxiplex were conducted, including bioadhesiveness testing (viscometry, coatability).

Biocompatibility

The Sponsor performed preclinical biocompatibility tests on Oxiplex in accordance with ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing. Table 6.1 summarizes the results.

Table 1: Biocompatibility & Toxicity Testing

Test		Standard	Result
Sensitization	Maximization Sensitization	ISO 10993-10:1995	Pass
Irritation	Intracutaneous Reactivity	ISO 10993-10:1995	Pass
Implantation	Muscular Implant Test	ISO 10993-6:1995	Pass
Cytotoxicity	MEM Elution Assay	ISO 10993-5:1993	Pass
Systemic Toxicity	System Injection	ISO 10993-11:1993	Pass
	Subchronic Toxicity	ISO 10993-11:1993	Pass
Genotoxicity	AMES Test	ISO 10993-3:1992	Pass
	Chromosomal Aberration	ISO 10993-3:1992	Pass
Microbiology	Material Mediated Rabbit Pyrogen	USP 23 <151>: 1995	Pass
	Kinetic-Chromogenic Limulus Assay (LAL)	USP <85>current edition	Pass @ ≤0.06 EU/mL (CSF exposure)
	Hemolysis	ISO 10993-4: 2002	Pass

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Preclinical Performance

The Sponsor completed multiple animal studies for the purpose of evaluating the safety, biocompatibility, and performance of Oxiplex. The preclinical studies demonstrated that Oxiplex is safe and effective when used in the laminectomy/laminotomy site and covering the dura. Test animals that received Oxiplex treatment typically had normal histological evaluation of the epidural space including normal bone healing. In contrast, most of the surgery-only Controls showed histological abnormalities, including fibrosis and adhesions (Rodgers et al, 2003). Additional studies were performed to evaluate the effect of Oxiplex on dural repair. Dural incisions that were covered with Oxiplex showed normal dural healing by both gross and histological exam.

Preclinical Studies Conclusion

Preclinical laboratory testing (per applicable standards) has shown that Oxiplex is biocompatible, non-toxic, and performs as expected in preclinical animal models.

Sterilization and Packaging

Oxiplex is terminally sterilized by steam. The sterilization cycle was validated per ANSI/AAMI/ISO 11134 to meet a minimum sterility assurance level (SAL) of 10^{-6} . Validation of the sterile barrier system for Oxiplex was performed per ISO 11607. Package integrity, seal strength, and shipping tests all passed.

X SUMMARY OF CLINICAL STUDIES

A. Feasibility Study

A feasibility clinical study entitled, "Randomized Single-Blind, Multicenter Pilot Clinical Trial to Determine the Safety of Oxiplex/SP Gel for the Reduction of Postoperative Peridural Fibrosis and Related Symptoms Following Lumbar Disc Surgery," (Feasibility Study) was initiated in January 2001. The primary objective was to evaluate the safety of applying Oxiplex during single-level spinal laminectomy, laminotomy, and discectomy, performed to eliminate or reduce symptoms associated with acute or subacute unilateral herniation of a lumbar intervertebral disc, in subjects undergoing their first surgeries for such conditions.

The Feasibility Study was designed as a 3-month safety study with quality-of-life (QOL) assessments at 1, 3, 6 and 12 months using the LSOQ and the Oswestry Disability Index (ODI). Thirty-five (35) subjects were enrolled at four (4) investigational sites; 23 were treated with Oxiplex and 12 received surgery only. The 3-month safety evaluation final report was submitted in March 2002, the QOL assessments were completed in October 2002 and the database was locked in May 2003. A final report was filed with the FDA in November 2003.

The results of the Feasibility Study have been published by Kim et al (2003, 2004) and demonstrated that Oxiplex was safe postoperatively at 3 months. Also, the study confirmed the similarity between the ODI and LSOQ results and showed that the LSOQ scores were similar at 6 and 12 months (see Figure 7.1). When subjects entered the Feasibility Study with severe pain and leg weakness, the subsequent responses to treatment with Oxiplex were greater than in subjects having lower baseline pain (i.e., the greater the disability entering the Feasibility Study, the greater the subject benefit derived from Oxiplex). The Feasibility Study was not powered to demonstrate statistical significance in any efficacy measure.

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B. Pivotal Study

The pivotal clinical trial “Randomized, Third-Party Blinded, Multicenter, Clinical Trial to Determine the Safety and Effectiveness of Oxiplex/SP Gel for the Reduction of Pain and Symptoms Following Lumbar Disc Surgery” was conducted in the United States. There were no investigational sites outside the United States and no foreign clinical data were collected in this Pivotal Study.

This was a superiority study. Subjects were randomized intraoperatively to receive surgery plus Oxiplex (the Oxiplex group) or to receive surgery only (the Control group) after all eligibility criteria were satisfied.

Each subject enrolled in the study was followed for six months after surgery to evaluate safety and effectiveness. 352 subjects were enrolled at 29 investigational sites between October 2002 and October 2006.

Quality of Life assessments were completed at baseline and postoperatively using the Lumbar Spine Outcomes Questionnaire (LSOQ). The LSOQ is a multi-item, quality of life questionnaire designed to assess complex factors that are considered clinically relevant in evaluating treatment outcomes specific to lumbar pain. The instrument provides for the collection of information that is specific to pain and other disabilities associated with the lumbar spine.

The LSOQ was developed by a multicenter group of neurosurgeons and orthopedic surgeons in response to a request for applications by NIH and was validated as part of a multicenter, prospective, longitudinal study of subjects referred to a tertiary care neurological or orthopedic surgeon for evaluation and treatment of persistent lower back (lumbar) pain with and without leg pain (BenDebba et al. 2000, 2007).

The LSOQ yields separate composite scores for leg pain severity, back pain severity, physical symptoms and activities of daily living from subjects’ responses at designated time points (baseline, 1, 3, and 6 months). In addition, the LSOQ measures clinical significance (patient satisfaction), disability days and pain medication for lower back condition. The LSOQ may be administered via telephone, by mail or in the clinic setting.

The Sponsor elected to use the LSOQ for assessment of the effectiveness of Oxiplex in this Pivotal Study to measure multiple clinical outcomes after site-specific surgical therapy in patients undergoing laminectomy, laminotomy or treatment of herniated disks, and FDA agreed to allow the use of this validated QOL instrument.

Study Objectives

The primary objectives of this Pivotal Study were:

1. To evaluate the efficacy of Oxiplex/SP Gel in the reduction of postoperative pain and symptoms
2. To evaluate the safety of applying Oxiplex/SP Gel in lumbar disc surgery

Effectiveness Variables

The primary effectiveness variable was the improvement in leg pain from baseline to each follow-up visit (1, 3 and 6 months).

The secondary effectiveness objective was to evaluate pain, symptoms, disability,

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patient satisfaction, and QOL measures relevant to the postsurgical condition of subjects with back pain undergoing lumbar surgery.

Secondary effectiveness variables were the improvements from baseline (follow-up visit score minus baseline score) in:

1. back pain
2. leg weakness
3. physical symptoms
4. subject satisfaction
5. disability score
6. activities of daily living

Safety Variables

The primary safety variable was the occurrence of (treatment-emergent) adverse events, including surgical complications, categorized using the MedDRA coding system (Version 7.1).

The secondary safety variables were:

1. Changes in laboratory results, physical and neurological exam and vital signs throughout the study
2. Reoperations at the lumbar level
3. Use of concomitant therapies

Study Design

- The study was a randomized, third-party blinded, multicenter, pivotal clinical trial to evaluate the safety and efficacy of Oxiplex used to reduce postoperative pain and related symptoms following surgery for herniated lumbar disc at L4-L5 or L5-S 1.
- Subjects underwent pre-surgical eligibility evaluations, including an examination by a neurosurgeon or an orthopedic spine surgeon.
- Subjects underwent a second eligibility evaluation after the informed consent had been signed. In order to qualify, the subject's were required to have a significant level of pain and symptoms per the LSOQ.
- Subjects underwent a third eligibility evaluation at the time of surgery. Certain unanticipated intraoperative findings or events, as defined in the study protocol, could disqualify a subject from being randomized.
- Subjects completed the LSOQ self-assessment questionnaire preoperatively and at scheduled postoperative intervals via telephone or written contact at 1, 3 and 6 months following surgery.
- All subjects received surgery and were randomized in a 1:1 ratio to either be treated with Oxiplex/SP Gel ("Oxiplex" group) or to receive surgery only ("Control" group), according to a computer-generated paradigm, with balanced assignment across the study and on a per-center basis. Randomization occurred intraoperatively, following primary surgery and immediately prior to wound closure. Study subjects have not

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been informed of their group assignment unless it was specifically requested after all data was analyzed.

- It was not possible to use a placebo device; therefore, members of the immediate operative team could not be blinded to the treatment assignment. However, the subjects and all evaluators involved in the follow-up assessments were blinded to the treatment assignment for the duration of the study.
- All subjects were evaluated for safety at 1 month and 6 months and for effectiveness at 1 month, 3 months and 6 months following surgery. Subjects received follow-up evaluations at 1 and 6 months postoperatively for clinical assessments, including physical examination, lower extremity neurologic function, wound inspection and laboratory tests.
- Qualified Clinical Evaluators (CE) performed postoperative physical examinations. The CEs were medically trained professionals who were blinded to the subject study group assignments (i.e., not a part of the treatment team and, therefore, not present at the time of intraoperative randomization).
- A preplanned interim analysis was performed when at least 75% of the subjects had completed the 6-month LSOQ.

Subject Enrollment

352 subjects were enrolled in the study.

Study Duration

The total duration of this Pivotal Study was approximately five years. The IDE was conditionally approved by the FDA in April 2002. Subject screening was initiated in August 2002, and the first subject was enrolled in October 2002. Each subject was followed for safety and efficacy for six (6) months after surgery. The final subject was enrolled in October 2006 and completed the 6-month follow-up visit in March 2007.

Study Population and Eligibility Criteria

Adult males and females scheduled to undergo first surgical intervention for diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy were screened for enrollment in this Pivotal Study.

Subject Inclusion Criteria

Subjects eligible for this Pivotal Study were adults who met all of the following criteria:

- Scheduled to undergo first surgical intervention for diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy
- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level
- Significant pain and symptoms measurable by the Lumbar Spine Outcomes Questionnaire (LSOQ)
- Radiological evidence (MRI Study or CT/myelogram) of compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at a level compatible with clinical signs and symptoms;

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- Compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at the L4-L5 or L5-S1 level
- Males, females of non-childbearing potential or females who were not pregnant (at the time of enrollment) and agreed not to become pregnant for at least 30 days after surgery
- Sexually active females of childbearing potential who agreed to use a medically acceptable method of contraception
- 18 to 70 years of age
- Laboratory test results within normal limits, or deemed not to be of clinical significance by the investigator and sponsor jointly, for the following parameters:
 - Hematology [Complete Blood Count (CBC) with differential and platelet count]
 - Urinalysis [specific gravity, pH, color, appearance, Glucose, Protein, Ketone, Occult Blood, Bilirubin]
 - Chemistry Panel [Electrolytes, BUN, Creatinine, ALT/SGPT, AST/SGOT, Alkaline Phosphates, Glucose, Total Bilirubin]
- Subjects entering the Pivotal Study were required to have undergone a period of at least two weeks of non-operative treatment without resolution of pain, unless the surgeon decided the subject was experiencing intractable pain or there was substantial progression of loss of neurological function
- Informed consent signed by the subject prior to surgery and any study specific procedures
- Subjects were able and willing to participate voluntarily in the Pivotal Study, including promised compliance with all Pivotal Study follow-up visits and evaluations

Subject Exclusion Criteria

Subjects who met any of the following criteria were not eligible for enrollment:

- Previous spinal surgery or chemonucleolysis at the lumbar level
- Treatment with any epidural steroids within four (4) weeks prior to the proposed surgery
- Use of steroids perioperatively and/or intraoperatively
- Presence of scoliosis; (> 10 degrees and considered by the investigator to be clinically significant)
- Presence of foraminal stenosis
- Known history of collagen-vascular or auto-immune disease (eg, rheumatoid arthritis, systemic lupus erythematosus), bleeding abnormalities, chronic debilitating disease, or malignancy within 5 years (except basal cell carcinoma)
- Myelogram or lumbar puncture for any reason within 24 hours prior to the proposed surgery
- Presence of any immunodeficiency disease, uncontrolled diabetes, or any systemic condition which, in the surgeon's opinion, may influence the outcome of the proposed surgery or postoperative period

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- Pregnant at the time of Pivotal Study enrollment
- Prisoner
- History of analgesic abuse/addiction
- Subject of a current or anticipated worker's compensation claim for any reason and/or party to a current or anticipated personal injury litigation for any reason
- Participation in any other clinical study involving an investigational device or drug within the 30 days immediately preceding enrollment in the Oxiplex/SP Gel Pivotal Study
- Any known condition or circumstance, which would prevent completion of the Pivotal Study or interfere with interpretation of the Pivotal Study results

Intraoperative Exclusions

Subjects who met any of the following criteria were not eligible for enrollment:

- Dural entry during surgery
- Discovery of intraspinal tumor during surgery
- Required spinal fusion
- Multilevel herniation, or the need to involve more than one level
- Exploration of contralateral side
- Epidural fat placement
- Use of steroid solutions
- Surgical determination that a hemostatic agent must remain at the surgery site
- Surgical determination of the need for any other device (that would interfere with interpretation of the Pivotal Study results) to remain at the surgery site

Study Procedures and Evaluations

Safety Assessments

Safety assessments included:

- physical examination (including wound assessment)
- the adequacy of wound healing, at 1 and 6 months postoperatively
- absence of wound dehiscence
- absence of wound infection
- the extent of irritation (pain and tenderness) at the wound site
- clinical neurologic evaluations of the spine and lower extremities
- clinical neurologic evaluations were related to motor or sensory deficit and abnormal reflexes and were determined preoperatively and at postoperative evaluations at 1 and 6 months. The incidence of complications/adverse events that were related to surgery or the wound site, as well as those that were unrelated to the procedure.
- clinically significant changes in laboratory test results

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Efficacy Assessments

The following instrument for assessing clinical response was used:

- Tabulated results of the subject LSOQ self-assessment questionnaires relating to pain, physical symptoms, weakness in the lower extremity and activities of daily living (ADL).
- A self-assessment questionnaire (LSOQ) was completed by the subject preoperatively and postoperatively at 1, 3 and 6 months. Mean scores for each composite measure were then determined for the Oxiplex and Control groups at each evaluation visit, including the preoperative evaluation. The scores allowed confirmation of the similarity between the Oxiplex and Control groups.

Preoperative Evaluations

- Subject's preoperative general evaluation, including personal history, pain evaluation, a functional evaluation and a list of the types of medication and other therapy regularly taken by the subject within the month prior to surgery.
- Surgeon's preoperative medical evaluation and diagnosis, recording the findings of a physical examination of the spine and lower extremities, including neurologic function status, review of radiographs, review of laboratory results (hematology, serum chemistries and urinalysis) and subject pain behavior.
- Sign Informed Consent.
- Subject completion of baseline LSOQ after Informed Consent had been signed. The site Study Coordinator reviewed responses with the potential participant to ensure that all questions had been answered. Copies of completed pages 1 and 2 were sent to FzioMed's Director of Clinical Affairs. The LSOQ pain and symptoms composite scores were determined by Clinical Affairs using the method described by BenDebba et al (BenDebba and Long, 2000; BenDebba, Heller, Ducker and Eisinger, 2001). Notification to the site documented whether the subject had met the LSOQ eligibility criteria.

Surgical Procedures and Evaluations

- Standard midline or paramedian approach.
- Removal of some or all of disc from the intervertebral location.
- Establishment of hemostasis and removal of iatrogenic hemostatic agents.
- Irrigation and aspiration prior to application of Oxiplex /SP Gel in treated subjects and before closure in all subjects.
- Completion of the Surgery Worksheet for required entries to this point of the procedure.
- Determination that the subject met the criteria for randomization.
- Determination of the randomization assignment: the subject was assigned to the Treated group or the Control group.
- [Oxiplex group only] The dura and exiting nerve root along both its dorsal and ventral surfaces were coated. The gel was applied into the site of the

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laminectomy/laminotomy to fill depth of the surgical site to the level of the ventral surface of the vertebral lamina. The volume delivered was not to exceed 3 mL.

- Closure of the wound in routine fashion.
- Completion of the remainder of the Surgery Worksheet.
- Site notification of subject enrollment to FzioMed, Inc. (via e-mail or FAX): subject initials, study subject identification number, surgery date and time of randomization/enrollment.

Follow-Up Evaluations

- Postoperative clinical assessments were performed at 1 month (3-6 weeks) and 6 months (22-28 weeks).
- The CE postoperative assessments at each of the scheduled visits were identical. A source document worksheet was provided for each visit. Each evaluation session included:
 - A physical examination, including the lumbar spine and lower extremities, motor/sensory function, and an evaluation of the wound site;
 - An assessment of adverse events;
 - A review of laboratory test results for clinical significance (hematology and serum chemistries at 1 and 6 months; urinalysis 1 month).
 - Self-assessment questionnaires were completed by the subject via telephone (or mail). The questionnaire was to be completed according to the Schedule of Evaluations shown in Table 2. The interviewer and subject remained masked concerning the study group assignment throughout the study.

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Table 2. Schedule of Evaluations

Assessment	Visit				
	Preop.	Surgery	Postop.	Postop.	Postop.
			30 Days (3-6 weeks)	3 Months (10-14weeks)	6 Months (22-28 weeks)
Informed Consent	X				
Medical History/Demographics	X				
Eligibility Assessment	X	X			
Enrollment/Randomization		X			
Lumbar Spine Outcomes Questionnaire	X ⁵		X	X	X
Physical Exam	X		X		X
Vital Signs	X		X		X
Hematology ¹	X		X		X
Chemistry ²	X		X		X
Pregnancy Test ³	X				
Urinalysis ⁴	X		X		
Concomitant Therapy	X	X	X	X	X
Adverse Events	X ⁶	X	X	X	X

1 Hematology: Complete Blood Count (CBC) with differential and platelet count.

2 Chemistry: Electrolytes, BUN, Creatinine, ALT/SGPT, AST/SGOT, Alkaline Phosphatase, Glucose, and Total Bilirubin.

3 Pregnancy Test: required for females of childbearing potential.

4 Urinalysis: specific gravity, pH, color, appearance, Glucose, Protein, Ketone, Occult Blood, Bilirubin.

5 Baseline LSOQ completed by subject *after* the Informed Consent had been signed. Following completion of questionnaire, site reviewed responses and forwarded pages 1 & 2 of the completed LSOQ via FAX to FzioMed Clinical Affairs (or telephoned Clinical Affairs to report the responses). Clinical Affairs determined the significance scores for pain and symptoms. The site was notified (via e-mail or FAX) if subject met the LSOQ eligibility criteria.

6 Preop/baseline medical conditions that were ongoing at the time of randomization/enrollment were to be documented.

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Study Demographics

As shown in Table 3, there were no significant differences between the Oxiplex group and the Control group in demographic characteristics at baseline

Table 3. Demographic Variables

Characteristic Continuous Covariate Measures	Oxiplex	Control	P-value*
	Mean (SD) N Median (Min, Max)	Mean (SD) N Median (Min, Max)	
Age	41.81 (10.53) 177 41.0 (21.0, 72.0)	41.71 (10.66) 175 42.0 (22.0, 67.0)	0.9278
Height (m)	1.73 (0.10) 177 1.73 (1.52, 2.03)	1.72 (0.10) 175 1.70 (1.52, 1.98)	0.6286
Weight (kg)	85.30 (19.10) 177 84.2 (51.8, 147.2)	83.13 (20.43) 174 82.5 (38.79, 137.3)	0.2574
BMI	28.45 (5.84) 177 27.2 (18.2, 48.4)	27.75 (5.55) 174 27.0 (11.9, 42.9)	0.4300
Pulse	74.21 (9.84) 175 74.0 (50.0, 107.0)	75.48 (10.63) 168 76.0 (52.0, 105.0)	0.2563
Blood Pressure Systolic	125.88 (16.86) 176 124.0 (90.0, 173.0)	124.60 (15.82) 169 122.0 (90.0, 186.0)	0.4585
Diastolic	78.53 (10.75) 176 80.0 (40.0, 115.0)	77.76 (9.70) 169 80.0 (56.0, 110.0)	0.3053
Respiration	16.61 (2.45) 167 16.0 (12.0, 24.0)	16.51 (2.73) 167 16.0 (12.0, 24.0)	0.9007
Categorical Measures	n/N (%)	n/N (%)	P-value**
Gender (Male)	87/177 (49.15)	98/175 (56.00)	0.2025
Race			
Caucasian	152/177 (85.88)	153/175 (87.43)	1.0000
African American	9/177 (5.08)	4/175 (2.29)	
Hispanic	8/177 (4.52)	11/175 (6.29)	
Asian	2/177 (1.13)	3/175 (1.71)	
Other	6/177 (3.39)	4/175 (2.29)	

*Two-sided two sample Wilcoxon Rank Sum test.

**Two-sided Fisher's exact test.

Blinding/Masking

It was not possible to use a placebo device; therefore, the members of the immediate operative team were not blinded. Thus, the following procedures were undertaken in order to maintain blinding for all ratings and assessments made on study subjects:

- The study was third-party blinded, in which the subject and evaluators of data were not informed of the randomization assignment during the course of the study.
- A qualified, medically trained person, assigned to the study to serve as a Clinical Evaluator (CE), performed postoperative lumbar examinations. Evaluations were performed under the supervision of the principal investigator. The principal investigator signed an authorization form verifying the evaluator's qualification and that the CE has been trained in the appropriate technique. The CE remained blinded to the subjects' treatment status throughout the study. The CE performed the physical examination (including the neurological assessment) at each study visit and

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completed the applicable source document worksheets. The worksheets listed the protocol-specific examinations that were performed. The CE was not a part of the treatment team who performed the surgery and randomization. Clinical Evaluators received the worksheets from the coordinator prior to the subject's scheduled visit. The CE returned the form to the coordinator and was NOT be permitted access to the subject's full CRF binder. Note: the CE and study coordinator may have been the same person provided the study coordinator remained blinded to the subject study group assignments.

- The investigator and site study coordinator agreed not to discuss the treatment assignments during the course of the study, or provide any documents to the subject or evaluators, which may reveal the assignment (e.g., an Operative Report.) At the time the subject completed the study, the subject signed a document confirming the maintenance of the subject blind, which will be filed in the subject's study binder. For data entry purposes, the study completion CRF noted compliance/non-compliance.
- Subjects were contacted via telephone or mail to complete the self-assessment questionnaires. Independent contractors who are masked to the treatment assignment made the contact.
- Sequentially numbered sealed boxes (with a subject identification number) were provided to each site. The boxes contained either Oxiplex/SP Gel (treatment) or an empty, non-sterile syringe (control). The control group boxes mimicked by appearance, weight and feel those boxes containing Oxiplex/SP Gel. The boxes were stored in a locked area until use. At the time of surgery the (lowest available numbered) box was delivered to the surgical suite. It was opened at the time of randomization after intraoperative eligibility has been determined. If the subject was not eligible, the unopened box was returned to the storage area and used for the next subject.

Summary of Safety

- Safety was assessed in all randomized subjects who were enrolled in this study (ITT population, N=352). Oxiplex was safe and did not expose patients undergoing lumbar surgery to additional risk.
- One (1) reoperation occurred in the Oxiplex group, while six (6) reoperations occurred in the Control group (P=0.0665). Five of the six subjects in the Control group who underwent reoperations had severe back pain at baseline. No Oxiplex subjects who had severe back pain at baseline had a reoperation.

Table 4. Percentage of Subjects with a Reoperation 0-6 months

	P-value*	Oxiplex N (%)	Control N (%)	Total Subjects N (%)
Subjects Randomized	0.1902	177	175	352
Re-operation 0-3-months	0.0665	1 (0.6%)	6 (3.4%)	7 (2.0%)
Re-operation 3-6 months**	N/A	0	0	0

*P-value is for Oxiplex vs. Control and is by the Fisher's Exact test

**All reoperations occurred by 3 months following the primary surgery.

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- There were no significant differences in the number of subjects having adverse events (AEs) or serious adverse events (SAEs) between the Oxiplex and Control groups.
- There were no AEs leading to discontinuation of the Pivotal Study or discontinuation of any subject from the Pivotal Study.
- There were no significant differences between the Oxiplex group and the Control group with respect to laboratory values (hematology, chemistry and urinalysis) and vital signs.
- Physical examinations at 1-month follow-up and at 6-month follow-up revealed clinical differences in favor of Oxiplex.
- Postoperative neurological examinations revealed that muscle spasms, pain in extremities and hypoaesthesia were reported less frequently in the Oxiplex subjects.
- There was comparability between concomitant therapies received by the Oxiplex group and the Control group.

The following tables summarize the safety data obtained in the U.S. Pivotal Study:

- Table 5. Analysis of AEs with Incidence $\geq 5\%$
- Table 6. Overall Incidence (%) of Serious Treatment Emergent Adverse Events by MedDRA System Organ Class
- Table 7. Abnormal Physical Examination at 1-Month Follow-Up
- Table 8. Abnormal Physical Examination At 6-Months Follow-Up Overall Incidence (%) of Treatment Emergent AEs Related To Incision Site

The results of this Pivotal Study provided reasonable assurance that Oxiplex is safe for its intended use.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Table 5. Analysis of AEs with Incidence \geq 5%

Incidence occurring \geq 5 %	Oxiplex	%	Control	%	Total Subjects	%
Subjects Randomized	N=177		N=175		N=352	
Subjects Reporting Any Adverse Event	n=163		n=153		n=316	
System Organ Class Preferred Term						
Gastrointestinal Disorders						
Constipation	12	6.8%	6	3.4%	18	5.1%
Nausea	35	19.8%	36	20.6%	71	20.2%
Vomiting	10	5.6%	9	5.1%	19	5.4%
General Disorders & administrative site conditions						
Chills	8	4.5%	8	4.6%	16	4.5%
Pyrexia	8	4.5%	11	6.3%	19	5.4%
Injury, Poisoning, Procedural Complications						
Incision Site Complication	57	32.2%	69	39.4%	126	35.8%
Procedural Pain	56	31.6%	54	30.9%	110	31.3%
Musculoskeletal, Connective Tissue Disorders						
Arthralgia	12	6.8%	12	6.9%	24	6.8%
Back Pain	44	24.9%	39	22.3%	83	23.6%
Buttock Pain	12	6.8%	13	7.4%	25	7.1%
Intervertebral Disc Protrusion	4	2.3%	9	5.1%	13	3.7%
Muscle Spasm	25	14.1%	31	17.7%	56	15.9%
Muscular Weakness	9	5.1%	9	5.1%	18	5.1%
Musculoskeletal Stiffness	9	5.1%	5	2.9%	14	4.0%
Myalgia	6	3.4%	13	7.4%	19	5.4%
Pain in Extremity	26	14.7%	38	21.7%	64	18.2%
Nervous System Disorder						
Dizziness	10	5.6%	8	4.6%	18	5.1%
Headache	14	7.9%	12	6.9%	26	7.4%
Hypoesthesia	18	10.2%	26	14.9%	44	12.5%
Hyporeflexia	9	5.1%	4	2.3%	13	3.7%
Sensory Loss	4	2.3%	8	4.6%	12	3.4%
Psychiatric Disorders						
Insomnia	12	6.8%	7	4.0%	19	5.4%
Skin and Subcutaneous Tissue Disorders						
Pruritis	8	4.5%	6	3.4%	14	4.0%

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Table 6. Overall Incidence (%) of Serious Treatment Emergent Adverse Events by MedDRA System Organ Class

	Oxiplex n (%)	Control n (%)	Total Subjects n (%)
Subjects Randomized	177	175	352
Subjects With A SAE	13	14	27
System Organ Class			
Preferred Term			
Cardiac disorders	1 (0.6%)	1 (0.6%)	2 (0.6%)
Gastrointestinal disorders	1 (0.6%)	1 (0.6%)	2 (0.6%)
Hepatobiliary disorders	1 (0.6%)	0 (0.0%)	1 (0.3%)
Infections and infestations	5 (2.8%)	2 (1.1%)	7 (2.0%)
Cellulitis	1 (0.6%)	0 (0.0%)	1 (0.3%)
Pneumonia	1 (0.6%)	0 (0.0%)	1 (0.3%)
Wound infection	3 (1.7%)	2 (1.1%)	5 (1.4%)
Injury, poisoning and procedural complications	1 (0.6%)	4 (2.3%)	5 (1.4%)
Cerebrospinal fluid leakage	0 (0.0%)	1 (0.6%)	1 (0.3%)
Dural tear	0 (0.0%)	1 (0.6%)	1 (0.3%)
Hip fracture	0 (0.0%)	1 (0.6%)	1 (0.3%)
Incision site complication	1 (0.6%)	0 (0.0%)	1 (0.3%)
Nerve injury	0 (0.0%)	1 (0.6%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	1 (0.6%)	5 (2.9%)	6 (1.7%)
Nervous system disorders	2 (1.1%)	1 (0.6%)	3 (0.9%)
Headache	1 (0.6%)	0 (0.0%)	1 (0.3%)
Migraine	1 (0.6%)	0 (0.0%)	1 (0.3%)
Syncope	0 (0.0%)	1 (0.6%)	1 (0.3%)
Psychiatric disorders			
Respiratory, thoracic and mediastinal disorders	0 (0.0%)	1 (0.6%)	1 (0.3%)
Asthma	2 (1.1%)	0 (0.0%)	2 (0.6%)
Pulmonary embolism	1 (0.6%)	0 (0.0%)	1 (0.3%)
Surgical and medical procedures	1 (0.6%)	1 (0.6%)	2 (0.6%)
Cholecystectomy	1 (0.6%)	0 (0.0%)	1 (0.3%)
Spinal fusion surgery	0 (0.0%)	1 (0.6%)	1 (0.3%)
Vascular disorders	1 (0.6%)	0 (0.0%)	1 (0.3%)
Deep vein thrombosis	1 (0.6%)	0 (0.0%)	1 (0.3%)

Note: A treatment emergent adverse event is defined as an adverse event that started post randomization, or an adverse event that started pre randomization and increased in severity post randomization. Subjects reporting a particular adverse event more than once are counted only once for that adverse event.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Table 7. Abnormal Physical Examination at 1-Month Follow-Up

Body System**	P-value*	Oxiplex N (%)	Control N (%)	Total Subjects N (%)
Subjects Randomized		177	175	352
Subjects with Physical Ex		173	169	342
General Appearance	1.0000	10 (5.8%)	9 (5.3%)	19 (5.6%)
Ears, Eyes, Nose, Throat	0.1956	5 (2.9%)	10 (5.9%)	15 (4.4%)
Head, Neck, Thyroid	0.6820	2 (1.2%)	3 (1.8%)	5 (1.5%)
Lungs	1.0000	2 (1.2%)	2 (1.2%)	4 (1.2%)
Chest, Including Breasts	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)
Heart/Cardiovascular	0.1180	1 (0.6%)	5 (3.0%)	6 (1.8%)
Lymph Nodes	0.4942	0 (0.0%)	1 (0.6%)	1 (0.3%)
Abdomen	1.0000	5 (2.9%)	4 (2.4%)	9 (2.6%)
Genitalia	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anorectal	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal	0.0728	26 (15.0%)	39 (23.1%)	65 (19.0%)
Neurological (non-lower back)	0.2669	36 (20.8%)	27 (16.0%)	63 (18.4%)
Skin	0.4910	12 (6.9%)	8 (4.7%)	20 (5.8%)
Other	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)

*P-value is for Oxiplex vs. Control at 1-month and is from Fisher's exact Test

**Body systems are not mutually exclusive.

Table 8. Abnormal Physical Examination At 6-Months Follow-Up Overall Incidence (%) of Treatment Emergent AEs Related To Incision Site

Body System**	P-value*	Oxiplex N (%)	Control N (%)	Total Subjects N (%)
Subjects Randomized		177	175	352
Subjects with Physical Ex at 6-Mos		140	144	284
General Appearance	1.0000	7 (5.0%)	7 (4.9%)	14 (4.9%)
Ears, Eyes, Nose, Throat	0.4419	6 (4.3%)	10 (6.9%)	16 (5.6%)
Head, Neck, Thyroid	1.0000	2 (1.4%)	3 (2.1%)	5 (1.8%)
Lungs	0.4983	0 (0.0%)	2 (1.4%)	2 (0.7%)
Chest, Including Breasts	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)
Heart/Cardiovascular	0.2140	1 (0.7%)	5 (3.5%)	6 (2.1%)
Lymph Nodes	1.0000	0 (0.0%)	1 (0.7%)	1 (0.4%)
Abdomen	0.5366	6 (4.3%)	4 (2.8%)	10 (3.5%)
Genitalia	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anorectal	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal	0.0769	22 (15.7%)	35 (24.3%)	57 (20.1%)
Neurological (non-lower back)	0.3623	44 (31.4%)	38 (26.4%)	82 (28.9%)
Skin	0.4834	11 (7.9%)	8 (5.6%)	19 (6.7%)
Other	N/A	0 (0.0%)	0 (0.0%)	0 (0.0%)

*P-value is for Oxiplex vs. Control at 6-months and is from Fisher's exact test

**Body systems are not mutually exclusive.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Summary of Effectiveness

Effectiveness Overview

- All subjects were treated surgically and generally showed substantial improvement following surgery.
- Pain in spine surgery patients is complex with multifactorial conditions that can not be adequately characterized by univariate methods or simple models. Therefore, multivariate analysis was approved to assess effectiveness.
- A tabulation of unadjusted means showed an improvement in leg pain that favored Oxiplex but was not amenable to statistical testing by univariate methods. Multivariate analysis allowed for multiple clinical conditions to be included in tests of statistical significance.
- Across all 7 primary and secondary effectiveness measures, Oxiplex subjects had greater mean differences in improvement than Control subjects, demonstrating consistent clinical benefit from the use of Oxiplex.
- The most prominent gains in improvement for Oxiplex subjects were demonstrated at the 6-month follow-up visit in patients who enrolled with severe back pain before surgery (LSOQ score ≥ 63 at baseline).
- The improvements afforded by Oxiplex (at 6 months in subjects with severe baseline back pain) were statistically significant in both primary and secondary effectiveness variables (leg and back pain), in ITT and CC populations, as confirmed by regression and sensitivity analyses.
- The study yielded 7 sets of clinical and statistical evidence demonstrating that Oxiplex subjects had significant improvements in outcomes compared to surgery-only Control subjects:
 1. Reduced leg pain
 2. Reduced back pain
 3. Enhanced patient satisfaction
 4. Fewer neurological abnormalities (pain in extremity and hypoaesthesia)
 5. Fewer musculoskeletal abnormalities
 6. Fewer disability days
 7. Fewer reoperations

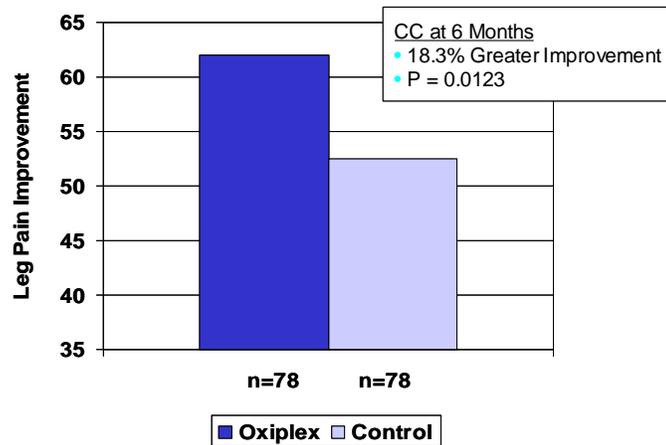
SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Effectiveness Results

- **Leg Pain:**

Oxiplex subjects in the CC population experienced 18.3% greater improvement in leg pain at 6 months relative to Control subjects (P=0.0123). The most prominent gain in improvement in the ITT population was also at the 6-month visit (13.6%, P=0.0507).

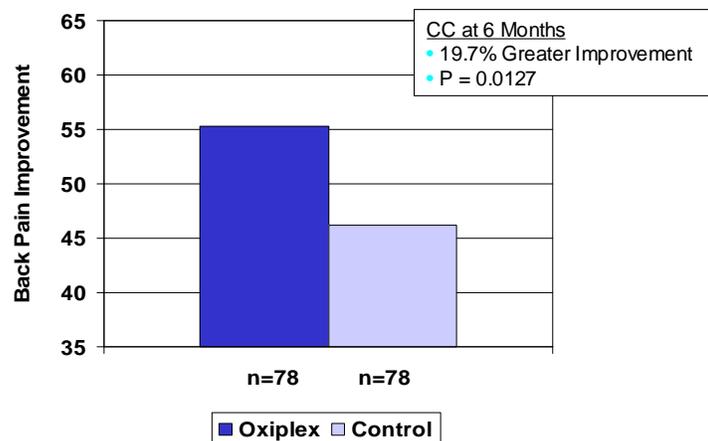
Figure 1. Improvement in Leg Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (CC)



- **Back Pain:**

Oxiplex subjects in the CC population experienced 19.7% greater improvement in back pain at 6 months relative to Control subjects (P=0.0127). The most prominent gain in improvement in the ITT population was also at the 6-month visit (17.1%, P=0.0193).

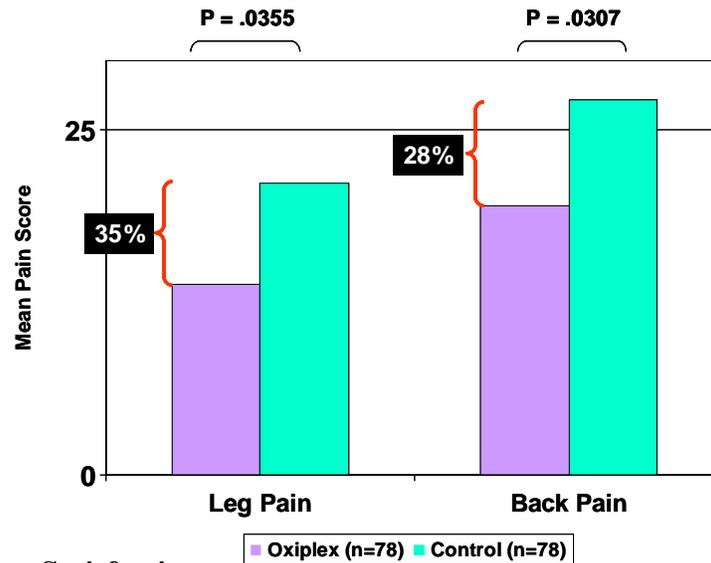
Figure 2. Improvement in Back Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (CC)



SUMMARY OF SAFETY AND EFFECTIVENESS DATA

These findings are clinically significant in that they represent additional measurable reductions in leg pain and back pain provided by Oxiplex in a challenging group of patients (those with severe back pain) versus surgery alone.

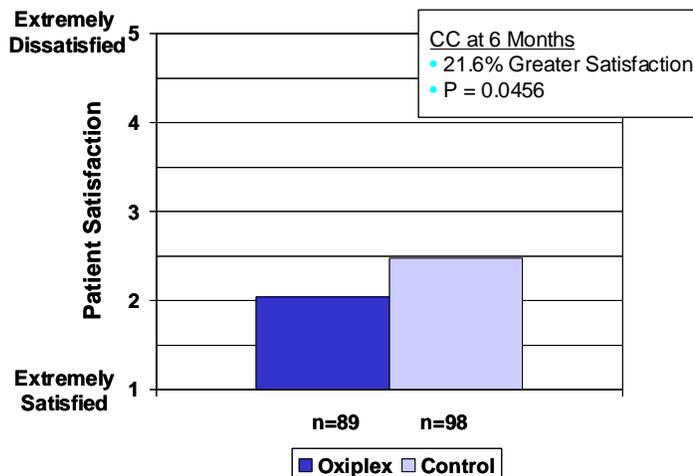
Figure 3 Additional Reduction in Leg and Back Pain at 6 Months in Subjects with Severe Baseline Back Pain



- Patient Satisfaction:**

Patient satisfaction is the LSOQ measure of clinical significance. Oxiplex subjects experienced 21.6% relative greater satisfaction at 6 months compared to Control subjects (P=0.0456).

Figure 4. Satisfaction at 6 Months by Treatment in Subjects with Severe Baseline Back Pain (CC) (SAR Figure 6.40)



SUMMARY OF SAFETY AND EFFECTIVENESS DATA

- **Reoperations (ITT):**

There were fewer reoperations in Oxiplex subjects (n=1, 0.6%) compared to Control subjects (n=6, 3.4%), a clinically significant improvement in patients with severe back pain at baseline.

- **Postoperative Neurological Abnormalities (ITT):**

Clinically significant improvements for Oxiplex subjects were also observed regarding postoperative neurological abnormalities. Oxiplex subjects had fewer findings of pain in extremity compared to Control subjects, especially at the 6-month study endpoint (Oxiplex group, n=26, 15%; Control group, n=38, 22%). Oxiplex subjects also had fewer findings of hypoesthesia compared to Control subjects, especially at the 6-month study endpoint (Oxiplex group, n=18, 10%; Control group, n=26; 15%).

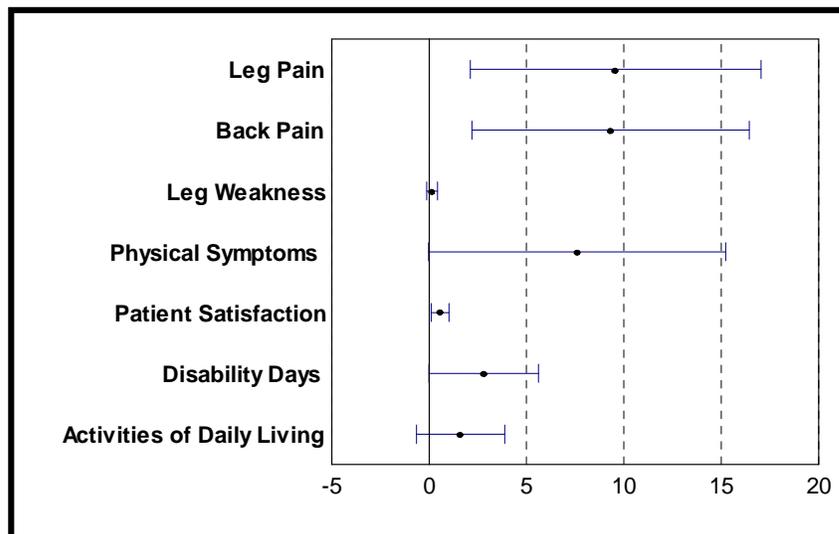
- **Disability Days:**

Disability days are defined as days when the subjects are completely disabled by their lower back conditions. Oxiplex subjects had fewer disability days than Control subjects (P=0.0497) at study end.

- **All Variables:**

For all effectiveness measures, Oxiplex subjects had greater mean differences in improvement compared to Control subjects. This demonstrated consistent clinical benefit of Oxiplex to reduce pain and symptoms following lumbar surgery in patients with severe baseline back pain.

Figure 1.5. Mean Differences in Improvement between Oxiplex and Control Groups at 6 Months for Subjects with Severe Baseline Back Pain (CC)



The results of this Pivotal Study provided reasonable assurance that Oxiplex is effective for its intended use.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Clinical Studies Outside the United States

No foreign clinical study data were included in the PMA for Oxiplex.

Surveillance Outside the United States

Fziomed has an established program to evaluate postmarket surveillance data outside the U.S. Since 2001, six (6) Post Market Surveillance Reports (based on over 100,000 units shipped over a 5-year period) have been received. Vigilance reports were filed with the Competent Authorities for each report. All reports were investigated by a team headed by a medical expert. In every case, it was concluded that the reports were not attributable to the device. All were reported to the Competent Authorities and have been closed.

Published Studies of Oxiplex (Oxiplex/SP Gel or MediShield)*

Results of preclinical and clinical studies on Oxiplex have been published in peer-reviewed journals and presented at medical congresses and scientific meetings, both in the U.S. and abroad.

A number of European surgeons have independently published or presented their experience using Oxiplex in spine surgery (see below). These reports from outside the United States support the conclusion that Oxiplex is safe and effective.

Table 9 summarizes the information that has been published.

Table 9. Published Studies of Oxiplex

Author	#Patients	Title / Results	Reference
P. Fransen (Belgium)	396	"Safety of carboxymethylcellulose / polyethylene oxide for the prevention of adhesions in lumbar disc herniation, a consecutive case series review."	Annals of Surgical Innov Res 2008;2(2)
P. Fransen (Belgium)	350	"Adhesion prevention in lumbar disc herniation: A retrospective review of 350 patients treated with carboxymethylcellulose/polyethylene oxide." Significant reduction in fibrosis using Oxiplex	American Association of Neurological Surgeons (AANS) 2007
A Agarwal (UK)	362	"Barrier gel: does it work in orthopedic surgery?" Significant reduction in peridural scarring, no adhesions of nerve to dura or annulus, no dural tears, as observed in second surgeries. Gel shown to be safe & to significantly inhibit peridural scarring.	Malaysia Orthopaedic Association (MOA) 2006
P. Fransen (Belgium)	246	"Adhesion prevention in lumbar disc herniation: A comparative study between fibrosis inhibitors." Oxiplex represents safer choice for fibrosis reduction in lumbar disc surgery than Adcon-L.	European Association of Neurological Societies (EANS) 2006

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

C. Gill (Germany)	40	<p>“Experience with Oxiplex/SP Gel for the prevention of post-surgical adhesions in decompressive spine surgery.”</p> <p>Compared to controls (no gel), Oxiplex/SP provided post-operative pain reduction by protection of neural structures & by decreasing scar formation and dural adherence. No wound healing problems, no neurological deficit with Oxiplex/SP.</p>	North American Spine Society (NASS) 2003
P. Simons (Germany)	270	<p>“Reduction of radiculopathy using MediShield anti-adhesion gel in spinal surgery.”</p> <p>Post-surgical residual radiculopathy lowest in MediShield group vs. Adcon-L & non-treated groups. The number of patients needing post-surgical therapy was lowest in MediShield group.</p>	Congress of Neurological Surgeons (CNS) 2004
G. Guizzardi et al (Italy)	30	<p>“Use of a novel gel-formulated anti-adhesion barrier for prevention of fibrotic adhesions in lumbar micro-discectomy procedures.”</p> <p>Controlled study comparing MediShield to control (no gel). No or negligible scar tissue evidenced in 73.5% of patients treated with Oxiplex/SP compared to significant scarring noted in non-treated controls. No complications or allergic reactions & no device-related adverse events.</p>	Congress of Neurological Surgeons (CNS) 2006
R Assietti et al (Italy)	70	<p>“Clinical experience with the use of MediShield gel for the prevention of peridural fibrosis.”</p> <p>Significantly better outcomes in MediShield-treated group vs. non-treated group.</p>	Congress of Neurological Surgeons (CNS) 2006
A De Meeus et al	82	<p>“Adhesion Prevention in Lumbar Disc Herniation with Oxiplex Gel. A Comparative Study with Adcon-L”</p> <p>Oxiplex represents a safe, less expensive alternative to reduce fibrosis without the negative side effects with Adcon-L.</p>	Belgian Society of Neuro Surgery, Annual Meeting, 2004

XI CONCLUSIONS DRAWN FROM STUDIES

The clinical data from this Pivotal Study and other independent studies support the conclusion that Oxiplex is reasonably safe and effective for its intended use.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

XII PANEL RECOMMENDATIONS

To be determined.

XIII CDRH DECISION

To be determined.

XIV APPROVAL SPECIFICATION

To be determined.