

DRAFT INSTRUCTIONS FOR USE/PACKAGE INSERT

CAUTION: Federal (U.S.) law restricts this device to sale by or on the order of a physician.

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

INDICATIONS

Oxiplex is indicated 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.

CONTRAINDICATIONS

Contraindicated for use in the presence of frank infection.

PRECAUTIONS

- Oxiplex must be used according to these 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.
- Any hemostatic agents 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.
- 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.
- 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.

HOW SUPPLIED

Oxiplex is provided sterile in a 3 mL syringe, along with a sterile, flexible applicator tip for use in applying Oxiplex during surgery. These components are packaged together in a thermoform tray, sealed with Tyvek® lid, and terminally sterilized by steam. The exterior of the sealed tray and lid are non-sterile. Oxiplex is for single use only. Unused Oxiplex should be discarded. Do not re-sterilize.

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STORAGE AND HANDLING

Oxiplex does not require refrigeration. Store at room temperature ($\leq 25^{\circ}\text{C}$).

INSTRUCTIONS FOR USE

A. Preparation

1. Remove tray containing the syringe and applicator from box.
2. The exterior of the tray is not sterile. Inspect the tray and lid to ensure they are not damaged or open. Do not use if the tray or lid have been damaged or opened.
3. The contents of the tray (syringe and applicator) are sterile. To maintain sterility, peel back the corner of the lid and place contents onto sterile field.
4. Using aseptic technique, remove syringe cap and discard.
5. Secure applicator to syringe.

B. Surgical Procedure

1. Follow standard technique for spinal laminectomy, laminotomy or discectomy surgery.
2. At the end of surgery and immediately prior to closing soft tissue incisions, achieve hemostasis.
3. Remove any hemostatic agent prior to applying Oxiplex.

C. Oxiplex Gel Application

1. Apply Oxiplex around exposed tissues, coating the dura and exiting nerve root along all surfaces (dorsal, ventral, medial and lateral).
2. Apply Oxiplex into the site of the laminectomy/laminotomy to fill the depth of the surgical site to the level of the ventral surface of the vertebral lamina.
3. Properly dispose of syringe and applicator after use.
4. Conclude the surgical procedure and close according to the standard technique of the surgeon.

CONTENTS

- 1 – Syringe, 3 mL (luer lock)
- 1 - Applicator tip (luer lock)
- 1 - Instructions for use with product tracking labels

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CLINICAL INVESTIGATIONS

A U.S. multicenter, randomized, third-party blinded, controlled clinical trial to determine the safety and effectiveness of Oxiplex for the reduction of pain and symptoms following lumbar disc surgery was conducted. A total of 352 patients were randomized to receive surgery plus Oxiplex (Oxiplex group n=177) or surgery alone (Control group, n=175). The effectiveness of Oxiplex was evaluated by the Lumbar Spine Outcomes Questionnaire (LSOQ) and by physical evaluations to assess improvement in clinical outcome measures including leg pain, back pain and neurological symptoms. The Completed Cases (CC) population is defined as subjects who completed the 6-month Lumbar Spine Outcomes Questionnaire.

SUMMARY OF SAFETY

- All subjects were treated surgically and generally showed improvement following surgery.
- Safety was assessed in all randomized subjects who were enrolled in this study (Intent-to-Treat or 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).
- 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.
- There was comparability between concomitant therapies received by the Oxiplex group and the Control group.
- The following tables contain data to support these findings:
 - Table 1. Analysis of AEs with Incidence $\geq 5\%$
 - Table 2. Overall Incidence (%) of Serious Treatment Emergent Adverse Events by MeDRA System Organ Class
 - Table 3. Abnormal Physical Examination at 1-Month Follow-Up
 - Table 4. Abnormal Physical Examination At 6-Months Follow-Up
 - Table 5. Reoperations

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Table 1. Analysis of AEs with Incidence ≥5% (ITT)

Incidence occurring ≥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%

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Table 2. Overall Incidence (%) of Serious Treatment Emergent Adverse Events by MedRA System Organ Class (ITT)

	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%)
	2 (1.1%)	0 (0.0%)	2 (0.6%)
Asthma	1 (0.6%)	0 (0.0%)	1 (0.3%)
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 before randomization and increased in severity post randomization. Subjects reporting a particular adverse event more than once are counted only once for that adverse event.

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Table 3. Abnormal Physical Examination at 1-Month Follow-Up (ITT)

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

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**Table 4. Abnormal Physical Examination At 6-Month Follow-Up
Overall Incidence (%) of Treatment Emergent AEs
Related To Incision Site (ITT)**

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

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Table 5. 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

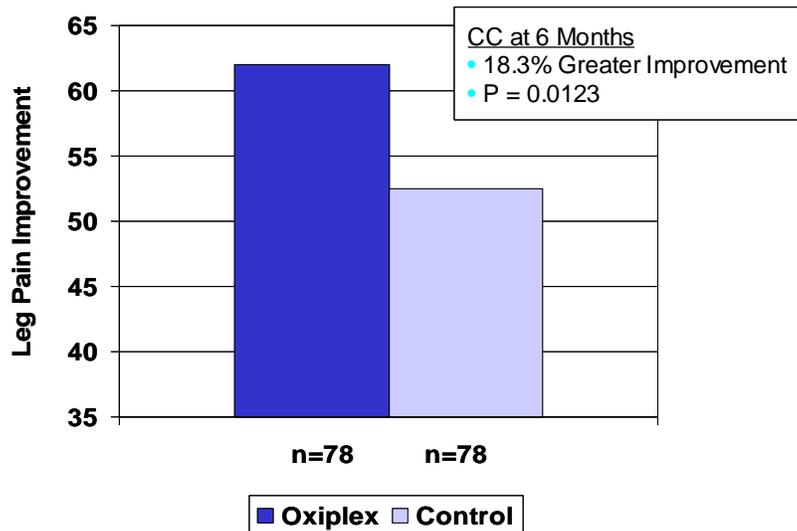
**All reoperations occurred by 3 months following the primary surgery.

SUMMARY OF EFFECTIVENESS

1. Primary Effectiveness Variable: Reduction in Leg Pain

- Improvement in leg pain (reduction from baseline) was evaluated, by multivariate longitudinal analysis, incorporating data from the three follow-up visits at 1 month, 3 months and 6 months.
- In the ITT population, the most prominent gain in improvement in leg pain by Oxiplex subjects was observed at the 6-month visit (P=0.0507) in subjects with severe back pain at baseline.
- The largest gain in improvement in leg pain by Oxiplex subjects in the CC population was observed at 6 months following surgery in subjects with severe back pain at baseline. This is shown in Figure 1.1.

Figure 1.1. Improvement in Leg Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (CC)



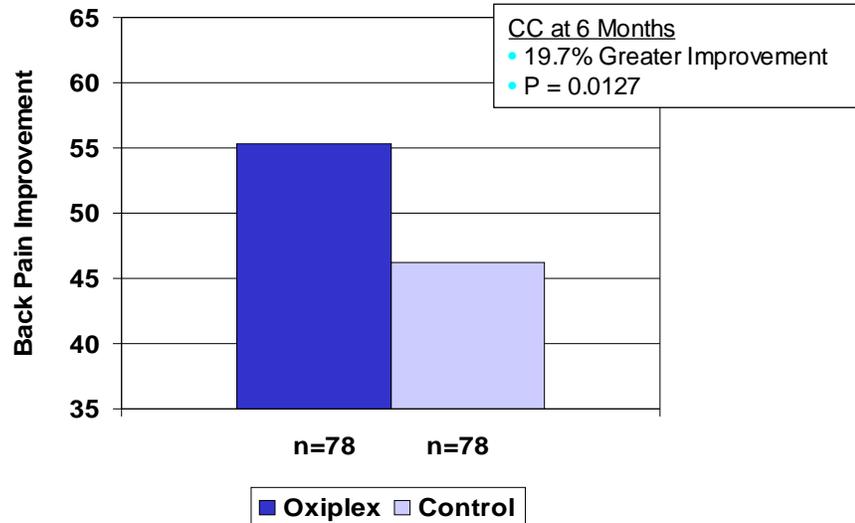
For subjects with severe back pain at baseline, there was an 18.3% relative reduction in leg pain score between the Oxiplex group and Control group at 6 months. This difference was both statistically (P=0.0123) and clinically significant (18.3%).

2. Secondary Effectiveness Variables

2.1. Back Pain

- Figure 2.1 shows the improvement in back pain from baseline at 6 months following surgery in subjects having severe baseline back pain.

Figure 2.1. Improvement in Back Pain from Baseline at 6 Months in Subjects with Severe Baseline Back Pain (CC)



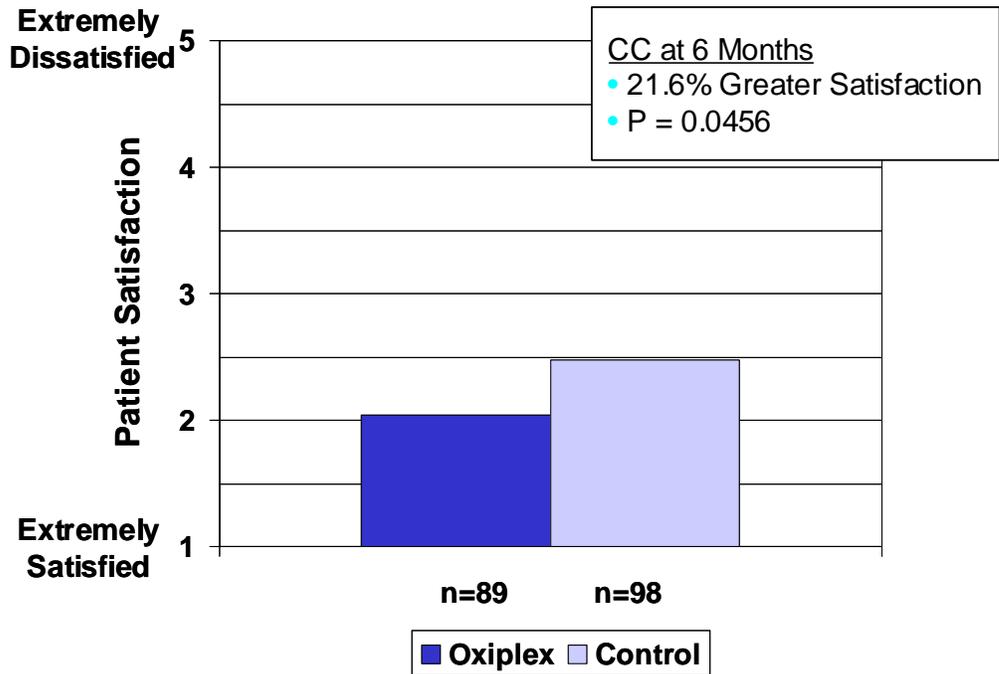
For subjects with severe back pain at baseline, there was a 19.7% relative reduction in back pain score between the Oxiplex group and Control group at 6 months. This difference was both statistically (P=0.0127) and clinically significant (19.7%).

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2.2. Patient Satisfaction (LSOQ Measure of Clinical Significance)

- Figure 2.2 shows patient satisfaction at 6 months by treatment for subjects having severe baseline back pain.

Figure 2.2. Patient Satisfaction at 6 Months by Treatment in Subjects with Severe Baseline Back Pain (CC)



Subjects with severe baseline back pain showed a 21.6% relative greater level of patient satisfaction in the Oxiplex group than in the Control group in the CC population as measured within 30 days of the 6-month evaluation. The difference was both statistically (P=0.0456) and clinically (21.6%) significant.

2.3. Reoperation (ITT)

- Seven (7) subjects required a reoperation for pain during the course of the study. Of the seven, six (6) subjects (3.4%) were from the Control group while only one (0.6%) was from the Oxiplex group.
- Five of the six subjects in the Control group who underwent reoperations had severe baseline back pain. No Oxiplex subjects who had severe back pain at baseline had a reoperation.

2.4. Disability Days (ITT)

- Disability days are defined as days when the subjects are completely disabled by their lower back conditions (i.e., days when the subjects remain immobile and inactive all or most of the time, e.g., in bed).

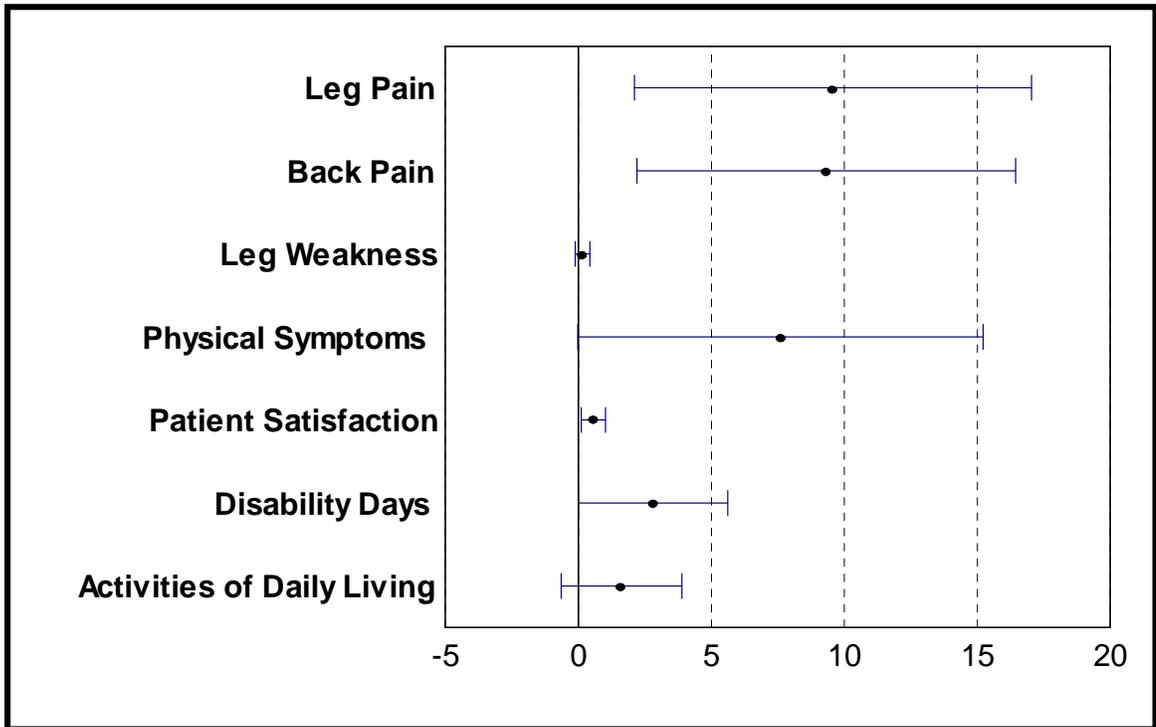
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- In the ITT population, Oxiplex subjects had fewer disability days relative to baseline than the Control group (2 fewer days, as measured over the last 30 days prior to the 6-month visit, P=0.0497, difference in means).

2.5. All Variables Among Completed Cases with Severe Back Pain:

- As shown in Figure 2.3, the mean differences in improvement from baseline between the treatment groups for all of the primary and secondary effectiveness variables for subjects with severe baseline back pain was greater for Oxiplex subjects than for Control subjects.

Figure 2.3. Mean Differences in Improvement between Oxiplex and Control Groups at 6 Months and Confidence Intervals for Effectiveness Measures for Subjects with Severe Baseline Back Pain (CC)



The figure displays the means (black dots) and 95% confidence intervals for the differences between Oxiplex treated and Control patients for each of the LSOQ variables. All seven of the variables showed a difference in favor of the Oxiplex group. The statistical likelihood that this would happen by chance alone is P=0.049, as determined by the O'Brien test (O'Brien, 1984). The mean improvements in leg pain, back pain and satisfaction for CC subjects at 6 months with severe baseline back pain in the Oxiplex group were statistically significant (confidence limit > zero). This demonstrated that Oxiplex was consistently effective at reducing pain and symptoms following lumbar surgery among patients with severe baseline back pain.

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3. Conclusions

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