



Data Suggest Cymbalta(R) Reduced Severity of Night Pain in Patients with Diabetic Nerve Pain

New Analysis Examines Impact of Pain on Sleep Interference

INDIANAPOLIS, May 3, 2007 /PRNewswire-FirstCall via COMTEX News Network/ -- Data from a pooled analysis of three studies suggest that in patients with pain caused by diabetic nerve damage, or diabetic peripheral neuropathy, who are treated with Cymbalta (duloxetine HCl), improvements in both average daily pain and night pain severity were associated with less pain-related sleep interference than in those patients taking sugar pill. Results from the analysis of more than 1,000 patients were presented today at the annual meeting of the American Pain Society in Washington D.C.

The average daily night pain severity and sleep interference correlation assessments were secondary analyses of data from trials in which the primary efficacy endpoint was to measure the reduction in average weekly pain. For these assessments, a subset of nonsomnolent patients was created by removing those who experienced treatment-related somnolence (such as daytime sleepiness, drowsiness, grogginess or difficulty awakening) or who were on other sedating medications. At the end of the 12-week analysis, this subset of patients treated with 60 mg of Cymbalta once- and twice-daily experienced significantly more improvement in 24-hour average pain scores than those taking sugar pill (47 percent, 50 percent and 29 percent respectively), as measured by reduction of scores on the self-reported, 11-point Likert scale.

In analyses of the effect of Cymbalta on night pain and pain-related sleep interference, nonsomnolent/nonsedating drug patients treated with 60 mg of Cymbalta once- and twice-daily experienced significantly more improvement in nighttime pain than those taking sugar pill after one week of treatment (22 percent, 21 percent and 10 percent, respectively) and at the end of the 12 weeks (47 percent, 51 percent compared with 34 percent). Both doses of Cymbalta reduced pain-related sleep interference at the end of the 12 weeks significantly more than sugar pill (55 percent, 57 percent and 45 percent respectively), as measured by the Brief Pain Inventory (BPI). No significant difference was seen between the 60 mg and 120 mg doses of Cymbalta.

Of greatest interest is the fact that for the first time, a clear correlation between reduction in average daily pain and average night pain and reduction in pain sleep interference was demonstrated in a population that was not depressed, did not experience treatment-emergent somnolence and was not on medications commonly associated with sedation. Other published studies of the relationship between pain and sleep interference have been confounded by at least one of those conditions.

"Patients with diabetic nerve pain often complain of being awoken, or having difficulty falling asleep because of pain, and it is difficult for physicians to know whether sleep problems are the cause or effect of pain," said David Fishbain, M.D., distinguished professor of psychiatry, adjunct professor of neurological surgery and anesthesiology at the University of Miami, and lead study author. "This new analysis is important because it suggests that interference with sleep generally improves if nighttime pain improves."

In this analysis, the most common adverse events experienced in the entire patient population as a whole were nausea, somnolence, dizziness, constipation, hyperhidrosis, dry mouth and decreased appetite. The median duration of nausea, somnolence and dizziness in Cymbalta-treated patients was six days, 14 days and five days, respectively, with the majority of patients who experienced these adverse events rating them as mild to moderate in severity. The overall discontinuation rate for patients on Cymbalta was 14 percent, while the overall discontinuation rate for patients on placebo was 7 percent. The most common adverse event cited as a reason for discontinuation was nausea (4 percent), followed by somnolence (2 percent), dizziness (2 percent), fatigue (1 percent) and vomiting (1 percent).

Methods:

Data were pooled from three double-blind, randomized, placebo-controlled, 12-week studies, to investigate associations between pain and sleep. In the first study, patients were treated with Cymbalta 20 mg once daily, 60 mg once daily, 60 mg twice daily and sugar pill. The second and third studies compared Cymbalta 60 mg once daily and 60 mg twice daily with sugar pill. A subset of nonsomnolent patients was created by removing patients reporting treatment-emergent somnolence or who were on sedating concomitant medications (No patients in any of the trials reported baseline somnolence.).

In the pooled data, the primary efficacy measure was the reduction in the weekly mean of the 24-hour average pain scores,

calculated from daily patient diary entries and measured by an 11-point Likert scale. Secondary measures included average daily night pain severity measured by an 11-point Likert scale and the BPI sleep interference item.

Patients with diabetic nerve pain who also had major depressive disorder (MDD) were excluded from this study, since depression could have had an effect on sleep interference, and improvements in depression could have improved sleep interference in these patients.(1,2,3)

Data on treatment-emergent adverse events, including reports of somnolence, were collected by spontaneous report, and while spontaneous reporting is the standard practice for evaluating treatments, solicited scales specifically designed for particular adverse events would have been preferable for the investigation.

About Diabetic Peripheral Neuropathy

According to the National Institute of Diabetes & Digestive & Kidney Diseases, approximately half of those with diabetes have some form of nerve damage, or neuropathy, but not all will develop symptoms. While nerve problems can occur at any time, the highest rates are among those who have had diabetes for at least 25 years. People who have had problems controlling their blood sugar levels, have high blood pressure, are overweight, have high levels of blood fat or are over the age of 40, may also have a greater risk of developing diabetic peripheral neuropathy. Symptoms can include numbness, tingling or pain and weakness in the toes, feet, legs, hands, arms and fingers. These symptoms are often worse at night.(4)

About Cymbalta

Serotonin and norepinephrine in the brain and spinal cord are believed to both help regulate the perception of pain and mediate core mood symptoms. Based on pre-clinical studies, duloxetine is a balanced and potent reuptake inhibitor of serotonin and norepinephrine that is believed to potentiate the activity of these chemicals in the central nervous system (brain and spinal cord). While the mechanism of action of duloxetine is not fully known, scientists believe its effect on pain perception, as well as its effects on depression and anxiety symptoms, may be due to increasing the activity of serotonin and norepinephrine in the central nervous system.

Cymbalta is approved in the United States for the treatment of major depressive disorder, the management of diabetic peripheral neuropathic pain and the treatment of generalized anxiety disorder, all in adults. Cymbalta is not approved for use in pediatric patients.

Important Safety Information

Cymbalta is approved to treat major depressive disorder, diabetic peripheral neuropathic pain and generalized anxiety disorder. In children and teens, antidepressants can increase the risk of suicidal thoughts or actions. Patients should call their doctor right away if they experience worsening depression symptoms, unusual changes in behavior or thoughts of suicide, especially at the beginning of treatment or after a change in dose. Cymbalta is approved only for adults 18 and over.

Cymbalta is not for everyone. Patients should not take Cymbalta if they have recently taken a type of antidepressant called a monoamine oxidase inhibitor (MAOI), are taking Mellaril(R) (thioridazine) or have uncontrolled glaucoma. Patients should speak with their doctor about all medicines they are taking, including those for migraine, to avoid a potentially life-threatening condition. Patients should tell their doctor about their alcohol consumption, if they have liver disease and about all of their medical conditions.

Patients taking Cymbalta may experience dizziness or fainting upon standing. The most common side effects of Cymbalta include:

- For MDD: nausea, dry mouth and constipation
- For DPNP: nausea, sleepiness and dizziness
- For GAD: nausea, fatigue and dry mouth.

This is not a complete list of side effects.

For full patient information, visit www.cymbalta.com.

For full prescribing information, including boxed warning, visit <http://www.cymbalta.com/>.

About Eli Lilly and Company

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the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

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This press release contains forward-looking statements about the potential of Cymbalta for the treatment of diabetic peripheral neuropathic pain and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. There is no guarantee that the product will continue to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

- (1) Goldstein DJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain*. 2005;116:109-118.
- (2) Raskin J, et al. A Double-Blind, Randomized Multicenter Trial Comparing Duloxetine with Placebo in the Management of Diabetic Peripheral Neuropathic Pain. *Pain Med*. 2005;6(5):346-356.
- (3) Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology*. 2006;67(8):1411-1420.
- (4) National Diabetes Information Clearinghouse. Diabetic Neuropathies: The Nerve Damage of Diabetes. National Institute of Diabetes and Digestive and Kidney Diseases.
<http://www.diabetes.niddk.nih.gov/dm/pubs/neuropathies/>, August 2004.

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