



Study Showed New Episodes of Depression Delayed in People Taking Cymbalta(R)

Fewer Patients on Treatment Experienced a New Episode

INDIANAPOLIS, IN, Dec 10, 2008 (MARKET WIRE via COMTEX News Network) -- New data suggest that Cymbalta (duloxetine HCl) 60 mg to 120 mg once daily delayed the onset of a new episode of depression in patients who had previously responded to the medication and who had recurrent depressive disorder, defined in the study as those patients who experienced at least three depressive episodes in the previous five years, compared with placebo ($p < .001$). Results from the 52-week maintenance phase of the longest controlled duloxetine study completed to date were presented at a meeting of a major scientific society today.

Additionally, patients who were treated with duloxetine were less likely ($p < .001$) to experience a new episode of depression than those who received placebo (recurrence rates were 14.4 percent vs. 33.1 percent, respectively).

Previous research has shown that up to 85 percent of patients with depression will experience depressive recurrences.(i) The number of episodes,(ii) their duration(iii) and the presence of lingering depressive symptoms increase the risk of recurrence, or future episodes of depression.(iv)

In the placebo-controlled maintenance phase of the study that followed initial open-label acute and continuation treatment phases, the most common adverse events (those occurring in at least 5 percent of patients in any treatment group) were headache, insomnia, dizziness, fatigue, back pain, common cold and flu.

Additional Study Findings

- Time to worsening of depressive symptoms was significantly longer ($p = .006$) in the duloxetine-treated group compared with the placebo-treated group. Worsening was defined as a 50 percent increase from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D17) total score and a Clinical Global Impressions of Severity (CGI-S) score of 3 or more at any time during the maintenance phase.
- Patients taking duloxetine experienced less worsening in symptom severity during the 52-week maintenance phase as measured by efficacy measures including the HAM-D17 total score and subscales, the CGI-S and the Patient's Global Impression of Improvement (PGI-I) scales, compared with those taking placebo (p -values $< .01$).
- Patients taking duloxetine experienced a similar worsening in somatic symptom severity during the 52-week maintenance phase as measured by Visual Analog Scales (VAS) for pain and the Symptom Questionnaire-Somatic Subscale (SQ-SS), compared with those taking placebo (p -values $> .05$).
- The proportion of duloxetine-treated patients who discontinued the study due to treatment-emergent adverse events during the acute, continuation and maintenance phases was 6.6 percent, 6.1 percent and 4.1 percent, respectively. Following were the most common treatment-emergent adverse events:
 - Acute phase: nausea, headache, dry mouth and excessive sweating
 - In addition, there was one person who did not complete the acute phase due to a completed suicide, which was determined by study investigators not to be attributed to treatment.
 - Continuation phase: headache, common cold and excessive sweating
 - Maintenance phase: headache, back pain and common cold

Methods

The 52-week maintenance phase was preceded by up to 34 weeks of open-label treatment with duloxetine 60-120 mg once daily. Of the 514 patients initially entered into the study, 288 patients met response criteria at the end of up to 34 weeks treatment and were entered into the 52-week, double-blind, maintenance phase of the study. During the maintenance phase, patients were randomly assigned to receive either duloxetine at the dose to which they had previously responded, or placebo.

The primary endpoint of the study was time to recurrence of a major depressive episode during 52 weeks of maintenance treatment, as assessed by any of the following recurrence criteria: a CGI-S score ≥ 4 and meeting DSM-IV criteria for major depressive disorder; three consecutive visits meeting re-emergence criteria or 10 total re-emergence visits; or study discontinuation due to lack of efficacy. Secondary measures included the HAMD17 total score and subscales, CGI-S and PGI-I scales, SQ-SS and VAS for pain. Safety and tolerability were assessed via analysis of treatment-emergent adverse events, vital signs, weight, ASEX for sexual functioning and laboratory measures. The primary study manuscript has already been submitted for review with a view to publication in a peer-reviewed medical journal.

About Duloxetine

Duloxetine is approved in the United States for the acute and maintenance treatment of major depressive disorder, the acute treatment of generalized anxiety disorder, and the management of diabetic peripheral neuropathic pain and fibromyalgia in adults aged 18 years and older. Duloxetine is not approved for use in pediatric patients.

Important Safety Information

Duloxetine is approved to treat major depressive disorder and generalized anxiety disorder, and to manage diabetic peripheral neuropathic pain and fibromyalgia. Antidepressants can increase suicidal thoughts and behaviors in children, adolescents, and young adults. Patients should call their doctor right away if they experience new or worsening depression symptoms, unusual changes in behavior, or thoughts of suicide. Be especially observant within the first few months of treatment or after a change in dose. Duloxetine is approved only for adults 18 and over.

Duloxetine is not for everyone. Patients should not take duloxetine 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 any medical conditions they may have including kidney problems, glaucoma, or diabetes. Patients should talk to their doctor if they have itching, right upper belly pain, dark urine, yellow skin or eyes, or unexplained flu-like symptoms, which may be signs of liver problems. Severe liver problems, sometimes fatal, have been reported. They should also talk to their doctor about alcohol consumption. Patients should tell their doctor about all their medicines, including those for migraine, to avoid a potentially life-threatening condition. Taking duloxetine with NSAID pain relievers, aspirin, or blood thinners may increase bleeding risk. Patients should consult with their doctor before stopping duloxetine or changing the dose and if they are pregnant or nursing.

Patients taking duloxetine may experience dizziness or fainting upon standing. The most common side effects of duloxetine include nausea, dry mouth, sleepiness, and constipation. This is not a complete list of side effects.

For full Patient Information, visit www.cymbalta.com.

For full Prescribing Information, including Boxed Warning and medication guide, visit www.cymbalta.com.

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This press release contains forward-looking statements about the potential of Cymbalta for the maintenance treatment of major depressive disorder, 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.

- (i) Mueller TI, Leon AC, Keller MB, et al. "Recurrence after recovery from major depressive disorder during 15 years of observational follow-up." Am J Psychiatry 1999;156:1000-1006.
- (ii) Maletic, V., et al. "Neurobiology of depression: an integrated view of key findings." Int J Clin Pract. 2007 Dec;61(12):2030-40.
- (iii) Ibid.
- (iv) Ibid.

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