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Eli Lilly and Company's Duloxetine Shown to Significantly Reduce Symptoms of Depression, Including Physical Symptoms

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Data on duloxetine, an investigational balanced serotonin and norepinephrine reuptake inhibitor, suggest superiority over placebo and paroxetine in reducing depressive symptoms. Additional data presented suggest superiority to placebo in reducing the physical symptoms associated with depression. The data were presented at the 14th Annual U.S. Psychiatric and Mental Health Congress in Boston, MA. Pain symptoms of depression, such as body aches and joint pain, are increasingly recognized as common manifestations of depression. These physical symptoms are often the impetus for depressed patients to seek treatment.

The studies also suggest duloxetine provides balanced, potent and tolerable effect at all doses, though the therapeutic evidence of duloxetine 60 mg/once daily dose was similar in magnitude to duloxetine 40 mg/taken twice a day (80 mg), indicating that a 60 mg/once daily dosing regimen can be used. The data are measured by mean change on the 17-item Hamilton Depression Rating Scale (HAMD₁₇).

"Duloxetine's dual mechanism of action offers the possibility for rapid onset of antidepressant effect, better response with pain symptoms and higher remission rates than available with SSRIs that are most commonly prescribed today," said John H. Greist, M.D., clinical professor of psychiatry, University of Wisconsin Medical School, who presented data on duloxetine at the congress. "Because we recognize that serotonin blockade alone is not sufficient for everyone, and that physical symptoms of depression often go unresolved, duloxetine may become a potent first-line antidepressant therapy."

Highlights of the four studies presented include:

- Duloxetine 60 mg once-daily dosing resulted in significantly greater reduction in HAMD₁₇ total score compared with placebo in two trials, respectively. (4.86 and 2.17)
- Duloxetine 60 mg/day statistically significantly reduced overall pain by the second week and back pain by the first week of active therapy.
- Duloxetine 60mg/day demonstrated up to a 112 percent increase in remission relative to placebo. Remission was defined as a score on the HAMD₁₇ of ≤ 7 .

In addition, one study of duloxetine 80 mg/day resulted in statistically greater reduction in HAMD₁₇ total score compared with paroxetine 20mg/day treated patients, (2.39) and placebo-treated patients (3.62). Duloxetine 80mg/day also demonstrated remission rates of 50 percent (versus 30 percent for placebo-treated patients) and statistically significantly reduced overall pain symptoms at end point. In the same study, paroxetine did not separate from placebo on this measure.

"Depression and physical symptoms such as pain may be mediated in the central nervous system through mechanisms involving serotonin and norepinephrine neurotransmitter pathways. Duloxetine's balanced effects on these neurotransmitters at starting clinical doses may result in rapid alleviation of both mood and physical symptoms associated with depression," said David Dunner, M.D., director of Center of Anxiety and Depression at the University of Washington and a presenter at the congress.

In clinical trials, duloxetine demonstrates a similar side effect profile to SSRIs. Discontinuation due to adverse events was similar to SSRIs (15 percent for duloxetine versus 5 percent for placebo). Additionally, there were no statistically significant differences among the duloxetine or placebo-treated patients in the incidence of sustained hypertension (0.7 percent for the duloxetine group and 0.4 percent for the placebo group).

Methodology

Four multi-center, parallel, randomized, double-blind, placebo-controlled studies involving outpatients with DSM-IV-defined major depressive disorder (MDD) were analyzed for duloxetine's efficacy in depression and associated physical symptoms.

Data results for the meta-analysis of duloxetine were derived from the following studies:

- 9-week primary efficacy study in which patients were randomly assigned to receive either duloxetine 60 mg (n=123) or placebo (n=122).
- 8-week dose response study in which patients were randomly assigned to receive duloxetine at daily doses of 40 mg (n=86), 80 mg (n=91), paroxetine 20 mg (n=87), or placebo (n=89).
- 8-week study in which patients were randomly assigned duloxetine titrated from 40 mg to 120 mg (n=68), placebo (n=66) or fluoxetine 20 mg (n=33) to assess assay sensitivity.
- 9-week study in which patients were randomly assigned duloxetine 60 mg (n=128) or placebo (n=139). Duloxetine was evaluated using the HAM-D₁₇, and for physical symptoms symptoms to depression using SSI pain subscales and pain visual analog scale (VAS) for overall pain severity.

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This press release contains forward-looking statements about the potential of the investigational compound duloxetine in treating depression that reflect management's current beliefs. However, as with any pharmaceutical under development, there are risks and uncertainties in the process of development and regulatory review. There are no guarantees that future clinical trials will confirm the preliminary results reported in this release or that the product will receive regulatory approvals or prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Exhibit 99 to the most recent Form 10-Q of Lilly dated November 2001.