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New Study Suggests Symbyax(R) Significantly Improves Symptoms of Treatment-Resistant Depression

INDIANAPOLIS, May 23, 2006 /PRNewswire-FirstCall via COMTEX News Network/ -- The results of a pooled analysis of two new parallel, randomized, double-blind studies suggest that Symbyax(R) (olanzapine and fluoxetine HCl capsules) significantly improved symptoms of treatment-resistant depression (TRD) when compared to either drug alone during a two-month period, based on the Montgomery-Asberg Depression Rating Scale (MADRS). Study results were presented today at a major medical meeting.

"Treatment-resistant depression is one of the greatest clinical challenges that psychiatrists face today, which is compounded by the fact that there is no FDA-approved medication for this illness," said Michael E. Thase, M.D., professor of psychiatry at the University of Pittsburgh Medical Center and the Western Psychiatric Institute and Clinic. "This is a rigorously designed study conducted in TRD patients who have not responded to two previous, adequately dosed antidepressants.

TRD is a condition in which some people with major depressive disorder (MDD) fail to sustain or achieve remission despite adequate antidepressant therapy. Adequate antidepressant therapy is defined as receiving an appropriate medication, at the proper dosage, for a suitable length of time.(i) Conservative estimates indicate that between 10 percent and 20 percent of MDD patients continue experiencing symptoms despite multiple treatments.(ii) The lack of effective medications for TRD can also lead to significant costs for the patient and their employers. Studies have shown that TRD led to substantial indirect costs to employers resulting from high rates of depression-associated disability.(iii)

Study Design (two identically designed trials)

Lead-in Period:

* 1,313 patients between 18 and 65 years of age who met DSM-IV criteria for recurrent major MDD without psychotic features were enrolled into an eight-week, open-label Prozac lead-in period.

* Patients could only be enrolled if they did not respond to an antidepressant (except Prozac) after at least six weeks of therapy at an adequate dosage during the current MDD episode.

* 605 patients did not respond to Prozac therapy.

Studies 1 and 2:

* 605 non-responders were randomized in these two eight-week, double- blind studies (Studies 1 and 2) and were assigned 1:1 to Symbyax (olanzapine 6, 12, or 18 mg/day plus fluoxetine 50 mg/day), Zyprexa alone (6, 12, or 18 mg/day), or Prozac alone (50mg/day). There were approximately 300 patients in each of the two studies.

* Mean modal doses (mg/day) for the double-blind studies were 8.6 and 48.8 for Symbyax (olanzapine and fluoxetine, respectively), 8.7 for Zyprexa alone, and 49.5 for Prozac alone.

* Of the 605 randomized patients, 441 patients (72.9 percent) completed the studies.

* A pooled analysis of both double-blind studies was conducted at the end of the eight-week trial period.

* TRD was defined as current episode antidepressant failure and prospective Prozac failure.

* Upward dose titrations were required at two-week intervals if no tolerability or safety issues were identified.

* The primary efficacy measure was improvement from baseline to endpoint on the MADRS.

Key Findings

Study 1:

* While all three treatment arms demonstrated improvements from baseline, this double-blind study showed no statistically significant differences in MADRS improvement among the three treatment arms (Symbyax: -10.8; Prozac: -9.4; Zyprexa: -10.1).

Study 2:

* This parallel double-blind study showed that patients taking Symbyax had average scores of -14.6 on the MADRS compared to Prozac (-9.0, $p < 0.001$) and Zyprexa (-7.7, $p < 0.001$) alone.

* Forty-four percent of the Symbyax patients responded to therapy, as opposed to 30 percent of Prozac patients and 17 percent of Zyprexa patients.

Pooled Analysis:

* Pooled results of both double-blind studies (Studies 1 and 2) showed significantly greater MADRS improvement for Symbyax (-12.6) versus Prozac (-9.2, $p < .001$) and Zyprexa (-8.9, $p < .001$) alone.

* Forty percent of Symbyax patients responded to therapy, as opposed to 30 percent of Prozac patients and 26 percent of Zyprexa patients.

* Within three to four days, Symbyax patients began to show significantly greater symptom improvement when compared to Prozac patients. At seven days, Symbyax also showed significantly greater symptom improvement when compared to Zyprexa.

* Adverse events in 10 percent or more of Symbyax patients were weight gain, increased appetite, dry mouth, somnolence, fatigue, headache, peripheral edema, hypersomnia, and tremor.

* Over the course of the study, the following changes occurred from baseline:

-- Mean weight change (kg) was +4.9 for Symbyax, +0.4 for Prozac, and +5.5 for Zyprexa ($p < 0.001$).

-- Cholesterol mean change (mg/dL) was +15.1 for Symbyax, +0.8 for Prozac, and +2.7 for Zyprexa ($p < 0.001$).

-- Triglyceride mean change (mg/dL) was +39.8 for Symbyax, +15.9 for Prozac, and +51.3 for Zyprexa ($p=0.040$).

Important Information on Symbyax

Suicidality in Children and Adolescents -- Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of SYMBYAX or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. SYMBYAX is not approved for use in pediatric patients.

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis -- Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-controlled patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure or sudden death) or infectious (eg, pneumonia) in nature. SYMBYAX is not approved for the treatment of elderly patients with dementia-related psychosis.

SYMBYAX should not be used with an MAOI or within at least 14 days of discontinuing an MAOI. At least 5 weeks should be allowed after stopping SYMBYAX before starting an MAOI. Thioridazine should not be given with SYMBYAX or within at least 5 weeks after stopping SYMBYAX. Concomitant use of SYMBYAX in patients taking pimozide is contraindicated.

Clinical worsening and suicide risk: All adult and pediatric patients being treated with an antidepressant for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially when initiating drug therapy and when increasing or decreasing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

Safety experience in elderly patients with dementia-related psychosis -- In placebo-controlled clinical trials of elderly patients with dementia- related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively). Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia -- Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus -- Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. All patients taking atypicals should be monitored for symptoms of hyperglycemia. Persons with diabetes who are started on atypicals should be monitored regularly for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Orthostatic hypotension -- SYMBYAX may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period. Particular caution should be used in patients with known cardiovascular disease, cerebrovascular disease, or those predisposed to hypotension.

Allergic events and rash -- In premarketing trials, the overall incidence of rash or allergic events with SYMBYAX was similar to that with placebo. In fluoxetine clinical studies, 7% of 10,782 fluoxetine-treated patients developed various types of rashes and/or urticaria. If rash or other possibly allergic phenomena appear for which an alternative etiology cannot be determined, immediate discontinuation is recommended.

Prescribing should be consistent with the need to minimize the risk of neuroleptic malignant syndrome, tardive dyskinesia, seizures, and orthostatic hypotension.

The most common treatment-emergent adverse event associated with SYMBYAX in placebo-controlled clinical trials was somnolence. Other common events were weight gain, increased appetite, asthenia, peripheral edema, tremor, pharyngitis, abnormal thinking, and edema.

For complete safety information, please see the full Prescribing Information at www.symbyax.com.

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This press release contains forward-looking statements about the potential of Symbyax for the treatment of treatment-resistant depression 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 prove 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) Rush, AJ, Crismon, ML, Toprac MG, et al. Consensus Guidelines in the Treatment of Major Depressive Disorder. J. Clin Psychiatry 1998; 59 (suppl. 20): 73-84.

(ii) Souery D., et al. Treatment-resistant depression: methodological overview and operational criteria. Eur Neuropsychopharmacol. 1999;9: 83-91.

(iii) Corey-Lisle, P. et al. Identification of a Claims Data "Signature" and Economic Consequences for Treatment-Resistant Depression. J Clin Psychiatry 2002; 63: 717-726.

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