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First Head-to-Head Study Shows Patients with Bipolar Depression Had Greater Symptom Improvement on Olanzapine and Fluoxetine HCl Capsules than Lamotrigine

ATLANTA, May 24, 2005 /PRNewswire-FirstCall via COMTEX/ -- New data from the first head-to- head study comparing olanzapine and fluoxetine HCl capsules (OFC) and lamotrigine for the treatment of bipolar depression, show that patients treated with OFC experienced significantly greater improvement in both depressive and manic symptoms associated with bipolar depression than patients treated with lamotrigine. Additionally, results show that patients treated with OFC responded more quickly to therapy than patients treated with lamotrigine. These findings were presented today at the annual meeting of the American Psychiatric Association.

Lamotrigine is not indicated for the acute treatment of bipolar depression; rather, it is indicated for the maintenance of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.

OFC is the first and only acute treatment approved by the U.S. Food and Drug Administration (FDA) for the depressive phase of bipolar disorder, a notoriously difficult-to-treat condition that afflicts millions of Americans. People with bipolar disorder typically spend an average of one-third of their lives in the depressive phase and take longer to recover from it. Patients with the disease have a higher risk of committing suicide than those with other psychiatric or medical disorders (1), and without effective treatment, bipolar disorder can lead to suicide in nearly 20 percent of cases.(2) The relative risk of suicide among patients with bipolar depression has been shown to be nearly 35 times greater than among patients in the manic phase of bipolar disorder.(3) However OFC is not indicated for the treatment of bipolar mania or bipolar maintenance.

"Bipolar depression is a devastating and debilitating condition that can wreak havoc on all aspects of a person's emotional, financial and social life, and often leads patients to take their own lives," said Doug Williamson, M.D., MRCPsych, US Medical Advisor, Eli Lilly and Company. "Providing symptom relief quickly is crucial in helping patients with bipolar depression."

Key Findings

In the double-blind 7-week trial, patients suffering from an acute episode of bipolar I depression were randomized to treatment with OFC (6/25, 6/50, 12/25, or 12/50 mg/day, n=205) or lamotrigine (200 mg/day; n=205). Patients were titrated to clinically effective doses as instructed by the products' labeling. Efficacy measures of improvement in both depressive and manic symptoms associated with bipolar depression included Clinical Global Impression Severity (CGI-S) as the primary outcome measure, as well as Montgomery-Asberg Depression Rating Scales (MADRS) and Young-Mania Rating Scale (YMRS).

Results showed:

* Patients treated with OFC had greater improvement than lamotrigine- treated patients across the 7-week treatment period when measuring CGI- Severity (p=0.002), MADRS total score (p=0.002) and YMRS (p=0.001);

* Time to response (50 percent decrease in MADRS scores) was significantly (p=0.010) shorter for patients treated with OFC.

In the study, serious adverse events, including symptoms associated with mania, occurred more frequently in patients treated with lamotrigine (5.4 percent vs. 1.0 percent; p=.012). Non-serious adverse events occurred more frequently ($p < .05$) with OFC treatment, including somnolence, weight gain and dry mouth.

About Bipolar Disorder

Bipolar disorder, sometimes referred to as manic depression, is a complex mental illness characterized by extreme and debilitating mood swings. These swings or "highs and lows" can range from episodes of deep depression marked by feelings of extreme guilt, sadness, anxiety, and, at times, thoughts of suicide; to episodes of mania (abnormal euphoria, elation and irritability) interspersed with periods of normal mood. Unlike many illnesses, symptoms may be quite different at various phases of the illness. Treatment is challenging because some therapies that are effective for one phase of bipolar disorder may be counterproductive for another. For example, antidepressant treatments can precipitate manic episodes.

More than 2.5 million Americans live with a diagnosis of bipolar disorder but recent research indicates the real number may be as high as 10 million. The results of untreated bipolar disorder can be catastrophic. The World Health Organization estimates that bipolar disorder is the sixth leading cause of disability in the world.

Important Information About Olanzapine-Fluoxetine HCl

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. Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. OFC is not approved for use in pediatric patients.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. OFC is not approved for the treatment of elderly patients with dementia- related psychosis.

The most common treatment-emergent adverse event associated with OFC (vs. placebo) in clinical trials was somnolence (22 vs. 11%). Other common events were: weight gain (21 vs. 3%), increased appetite (16 vs. 4%), asthenia (15 vs. 3%), peripheral edema (8 vs. 1%), tremor (8 vs. 3%), pharyngitis (6 vs. 3%), abnormal thinking (6 vs. 3%), and edema (5 vs. 0%).

Contraindications -- OFC 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 OFC before starting an MAOI. Thioridazine should not be given with OFC or within at least 5 weeks after stopping OFC. OFC is contraindicated in patients with known hypersensitivity to the product or any component of the product.

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.

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia -- Cerebrovascular adverse events (e.g., 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.

Orthostatic hypotension -- OFC 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 OFC was similar to that with placebo (4.6%, 26/571 vs. 5.2%, 25/477). 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.

Concomitant use -- Caution should be used when prescribing medications that contain olanzapine or fluoxetine HCl with OFC.

Abnormal bleeding -- Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of OFC with NSAIDs, aspirin, or other drugs that affect coagulation.

Mania/hypomania -- Because of the cyclical nature of bipolar disorder, patients should be monitored closely for the development of symptoms of mania/hypomania during treatment with OFC.

Prolactin and serum sodium -- As with other drugs that antagonize dopamine receptors, OFC elevates prolactin levels, and a modest elevation persists during administration; however, possibly associated clinical manifestations were infrequently observed. Hyponatremia has been observed in premarketing studies of OFC, but the incidence of serum sodium levels occurring below the reference range was statistically insignificant compared with placebo (2%, 10/500 vs. 0.5%, 2/380); none of these patients had a treatment-emergent level less than 130 mmol/L.

Transient, asymptomatic elevations of hepatic transaminase -- In premarketing trials, statistically significant ALT (SGPT) elevations (>/= 3 times the upper limit of the normal range) were observed in 6.3% (31/495) of patients exposed to OFC compared with 0.5% (2/384) of the placebo patients and 4.5% (25/560) of olanzapine-treated patients. None of these patients developed jaundice. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Weight gain -- In clinical studies, the mean weight gain for OFC-treated patients was statistically significantly greater than placebo-treated (3.6 kg vs. -0.3 kg) and fluoxetine-treated (3.6 kg vs. -0.7 kg) patients but was not statistically significantly different from olanzapine-treated patients (3.6 kg vs. 3.0 kg). Fourteen percent of OFC-treated patients met criterion for having gained > 10% of their baseline weight.

Special populations and elderly -- Dysphagia was observed infrequently in premarketing studies, but as with other psychotropic drugs, OFC should be used cautiously in patients at risk for aspiration pneumonia. Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. In 2 clinical studies in patients with Alzheimer's disease, 2 olanzapine- treated patients died from aspiration pneumonia, with one of these patients experiencing dysphagia. As with other CNS-active drugs, OFC should be used with caution in elderly patients with dementia. The lowest starting dose should be considered in patients with hepatic impairment.

As with all medications that contain an antipsychotic, the following considerations should be taken into account when prescribing OFC:

Neuroleptic malignant syndrome (NMS)-- as with all antipsychotic medications, a rare condition known as NMS has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended.

Tardive dyskinesia (TD) -- as with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

Seizures -- occurred infrequently in premarketing clinical trials (4/2066, 0.2%). Confounding factors may have contributed to many of these occurrences. OFC should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Such conditions may be more prevalent in patients age 65 years or older.

For prescribing information please visit www.lilly.com. P-LLY

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This press release contains forward-looking statements about the potential of Olanzapine and Fluoxetine HC1 capsules for the treatment of the depressive phase of bipolar 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 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.

(1) Jamison, KR. "Suicide and Bipolar Disorder." Journal of Clinical Psychiatry. 2000;61 (suppl 9).

(2) National Institute of Mental Health,
www.nimh.nih.gov/publicat/bipolarresfact.cfm.

(3) Tohen M, Vieta E, Calabrese J, Ketter T, Sachs G, et al. "Efficacy of Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar I Depression." Arch Gen Psychiatry. 2003;60:1079-1088.

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