Olanzapine Long-Acting Injection (LAI) Shown to Maintain Treatment Benefit in Schizophrenia for up to Six Months

BARCELONA, Spain, Sept 02, 2008 /PRNewswire-FirstCall via COMTEX News Network/ -- Final results from a 24-week study presented today at a major medical meeting in Barcelona suggest that investigational olanzapine long-acting injection (LAI) therapeutic doses showed a maintenance of treatment benefit for up to six months. A review of pooled safety data from all olanzapine LAI clinical trials was also presented at the meeting.

Olanzapine LAI is an investigational formulation that combines Zyprexa(R) (olanzapine), an atypical antipsychotic, with pamoic acid resulting in a salt that sustains the delivery of olanzapine for a period of up to four weeks. Long-acting injectable antipsychotics have been associated with improved treatment of schizophrenia in patients who have difficulty adhering to daily treatment regimens.(1)

"These studies offer insight into the role olanzapine LAI may play in the treatment of patients with schizophrenia who have benefited from olanzapine but continue to struggle with adherence," said David McDonnell, M.D., clinical research physician at Lilly. "If approved, olanzapine LAI could be a valuable treatment option due to the chronic and severe nature of schizophrenia, persistent challenges with adherence and the limited number of available depot formulations."

Independent regulatory reviews of olanzapine LAI applications are ongoing in the European Union, Canada, Australia and United States. Olanzapine LAI is currently being reviewed by CHMP and submission to regulators to obtain country-specific marketing approval is dependent upon a CHMP opinion.

Notes for editors:

About HGKA (24-week maintenance of effect study)

In this 24-week double-blind maintenance study, a total of 1,065 adult outpatients with schizophrenia who had been stabilized previously with open- label oral olanzapine (10, 15, or 20 mg daily) for four to eight weeks were randomized to one of three therapeutic dosing regimens of olanzapine LAI (150 mg every two weeks, 300 mg every two weeks or 405 mg every four weeks), to a low reference dose of olanzapine LAI (45 mg every four weeks), or remained on oral olanzapine at their previously stabilized dose. No supplementation with oral antipsychotics was permitted during the study.

An assessment of clinical stability was based on change in oral olanzapine dose as well as standard measures including Clinical Global Impressions- Improvement of Illness (CGI-I) and Brief Psychiatric Rating Scale (BPRS) scales. Symptom severity was assessed using the Positive and Negative Syndrome (PANSS), PANSS-derived BPRS, and the Clinical Global Impressions-Severity of Illness (CGI-S) and CGI-I scales.

Therapeutic doses of olanzapine LAI were shown to provide positive maintenance of treatment for up to six months. Mean baseline-to-endpoint changes in PANSS total scores for patients treated with therapeutic olanzapine LAI doses (150 mg every 2 weeks, 300 mg every 2 weeks and 405 mg every 4 weeks) differed significantly from those treated with the reference dose (respectively, 2.7, -2.2, -0.1, vs. 7.3; all $p<.001$). Significant separation in PANSS total scores was seen between the therapeutic doses (150 mg/two weeks, 300 mg/two weeks, 405 mg/four weeks) versus the reference dose (45 mg/four weeks) starting at 11, three, and two weeks, respectively, and maintained throughout the study ($p<.05$).

Similar differences between therapeutic and reference olanzapine LAI doses were observed for the BPRS total, CGI-I, and CGI-S scores. Mean baseline-to- endpoint change in PANSS total score for the oral olanzapine group (-1.7) did not differ significantly from that of the highest olanzapine LAI dose group (-2.2, 300 mg/2 weeks; $p=0.606$) but was greater than the other olanzapine LAI doses ($p<0.01$).

The safety profile for olanzapine LAI was consistent with that of oral olanzapine except for injection-related events. The rate of discontinuation was low over six months of treatment. Incidence of weight gain of 7 percent or more from baseline was significantly higher for patients treated with oral olanzapine (21.4 percent), olanzapine LAI 150 mg every two weeks (16.4 percent), olanzapine LAI 300 mg every two weeks (20.7 percent) and olanzapine LAI 405 mg every four weeks (15.2 percent) when compared with patients treated with olanzapine LAI 45 mg every 4 weeks (8.3 percent, all p less than or equal to .05). The incidence of all injection site reactions, including injection pain, was 2.8 percent. Adverse events reported in 5 percent or more of patients were insomnia, weight increase, anxiety, nasopharyngitis, somnolence and headache. In HGKA, two patients

experienced and recovered fully from Olanzapine LAI Post-Injection Syndrome, which includes a range of symptoms of sedation (ranging from mild in severity to unconsciousness) and/or delirium (including confusion, disorientation, agitation, anxiety and other cognitive impairment). Other symptoms include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion.

Earlier this year, data pertaining to the study's primary relapse endpoint was disclosed at the Schizophrenia International Research Society (SIRS) Conference. These data showed that patients treated with all three higher doses of olanzapine LAI had longer time to symptom exacerbation than patients who received the reference dose and that the four-week 405 mg and the pooled two-week dosing regimens showed non inferiority when compared to oral olanzapine and to each other.

About Olanzapine LAI Post-Injection Syndrome Analysis

As with all medications, there are risks associated with the use of long- acting injections. Across all olanzapine LAI clinical trials, olanzapine LAI showed a similar safety profile as the oral formulation except for injection- related events, including Olanzapine LAI Post-Injection Syndrome.

The purpose of this analysis was to review the Olanzapine LAI Post- Injection Syndrome cases observed in olanzapine LAI clinical trials to determine appropriate recommendations for risk and medical management. Safety data were pooled from all completed and ongoing olanzapine LAI clinical trials through 30 September 2007; adverse event data through 31 May 2008 were also reviewed.

As of 31 May 2008, the incidence of Olanzapine LAI Post-Injection Syndrome following administration of olanzapine LAI was 29 cases (in 28 patients) after more than 40,000 injections, yielding a per-injection rate of 0.07 percent and a per-patient rate of 1.4 per cent - or approximately one event per 1,400 injections. No clinically significant decreases in vital signs were observed and all patients recovered completely from signs and symptoms of Olanzapine LAI Post-Injection Syndrome within 1.5 to 72 hours. Approximately 70 percent of patients continued to receive injections after the event. The cumulative risk of experiencing an Olanzapine LAI Post-Injection Syndrome event after one year of treatment was 0.7 to 1.2 percent. (These data were presented as a range due to variable injection intervals).

Across all clinical trials, as of 31 July, no additional cases of Olanzapine LAI Post-Injection Syndrome were reported.

Based on the extensive review of pooled safety data from all olanzapine LAI clinical trials and given that awareness and recognition of these events are key aspects of identifying them and minimizing associated symptoms, Lilly has proposed a comprehensive plan for managing Olanzapine LAI Post-Injection Syndrome risks that includes a detailed product label including a post- injection observation period and an extensive healthcare provider training and educational program.

About Long-acting Injectable Antipsychotic Medications

The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines state that poor or partial treatment compliance is a major problem in the long-term treatment of schizophrenia. Depot formulations should be considered as a treatment option when a patient expresses a preference for such treatment due to convenience or if it is determined that a depot formulation is necessary to help avoid nonadherence to oral medications.(2)

Long-acting antipsychotic formulations have been associated with improved treatment adherence and reduced treatment failures.(3) By administering long- acting medications, healthcare professionals know when patients have received their medication and can immediately detect non-adherence when a patient fails to return for a scheduled injection.(4) Different from both oral and injected short-acting formulations, long-acting formulations of antipsychotics allow for stable concentrations of the active drug to remain at a therapeutic range for an extended period of time.(5)

About Schizophrenia

Schizophrenia is a severe and debilitating illness with symptoms such as delusions (false beliefs that cannot be corrected by reason), hallucinations (usually in the form of non-existent voices or visions), disorganized speech and severe disorganized or catatonic behavior. These signs and symptoms are associated with marked social or occupational dysfunction. Features of schizophrenia consist of characteristic signs and symptoms that have been present for a significant portion of time during a one-month period, with some signs of the disorder persisting for at least six months.(6) In addition to these symptoms, patients with schizophrenia are at greater risk for medical comorbidities than the general population.

About Olanzapine

Since olanzapine was introduced in 1996, it has been prescribed to approximately 24 million people worldwide. Olanzapine is not recommended for use in patients under 18 years of age.

In Europe, olanzapine is indicated for schizophrenia and in clinical trials, it has shown to be effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response. It is also indicated for the treatment of moderate to severe manic episodes and, in those patients whose manic episode has responded to olanzapine treatment, it is indicated for the prevention of recurrence in patients with bipolar disorder.

SAFETY INFORMATION

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported, which may be a predisposing factor. Appropriate clinical monitoring is advisable, particularly in diabetic patients and in patients with risk factors for diabetes mellitus for which regular glucose control is recommended.

Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline. Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders.

The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 4-6 months.

As with all antipsychotic medications, a rare and potentially fatal condition known as Neuroleptic Malignant Syndrome (NMS) has been reported rarely with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

Also, as with all antipsychotic treatment, prescribing should be consistent with the need to minimize Tardive Dyskinesia (TD). The risk of developing TD increases as the duration of treatment. If signs and symptoms of TD are observed a dose reduction or discontinuation should be considered and it should be noted that the symptoms can temporally deteriorate or even rise after discontinuation.

Other potentially serious adverse events include low blood pressure, seizures, elevated prolactin levels, elevated liver enzymes, thromobembolism, neutopenia, sweating, insomnia, tremor, anxiety, nausea, or vomiting.

Olanzapine should not be used in patients who have a hypersensitivity to the drug nor those with narrow angle glaucoma. It should not be used to treat dementia-related psychosis and/or behavioural disturbances because of an observed increase in death and cerebrovascular accident. It should also not be used in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease.

The most frequently (seen in greater than or equal to 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels, glucosuria, increased appetite, dizziness, akathisia, parkinsonism, dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic transaminases, rash, asthenia, fatigue and oedema.

About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.co.uk

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This press release contains forward-looking statements about the safety and efficacy of olanzapine long acting injection (LAI) and reflects Lilly's current beliefs. However, as with any investigational pharmaceutical product, there are substantial risks and uncertainties in the process of research, development, regulatory milestones and commercialization. There is no guarantee that olanzapine LAI will be approved for the treatment of schizophrenia or that if approved, it will 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) Maxine X. Patel and Anthony S. David. Why aren't depot antipsychotics prescribed more often and what can be done about it? Advances in Psychiatric Treatment (2005) 11: 203-211.

(2) Falkai P., Wobrock T., Lieberman J., Glenthoj B.,Gattaz W.F., Moller H.J. & Wfsbp Task Force On Treatment Guidelines For Schizophrenia. The World Journal of Biological Psychiatry, 2006; 7(1): 5/40

(3) Maxine X. Patel and Anthony S. David. Why aren't depot antipsychotics prescribed more often and what can be done about it? Advances in Psychiatric Treatment (2005) 11: 203-211.

(4) Kane J.M. et al. Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology, Volume 8, Number 1, 1 February 1998, pp. 55-66(12). p. 58.

(5) Maxine X. Patel and Anthony S. David. Why aren't depot antipsychotics prescribed more often and what can be done about it? Advances in Psychiatric Treatment (2005) 11: 203-211.

(6) American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, fourth edition, 2000, pp. 298.

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