Olanzapine Long-Acting Injection (LAI) Efficacy and Safety Data Presented at American Psychiatric Association Annual Meeting

--Three-year data show olanzapine LAI safety findings consistent with oral olanzapine except for injection-related events

INDIANAPOLIS, May 18, 2009 /PRNewswire-FirstCall via COMTEX News Network/ -- Eli Lilly and Company presented today data on the short- and long-term efficacy and safety of olanzapine long-acting injection (LAI) in the treatment of adults with schizophrenia or schizoaffective disorder. Olanzapine LAI is an investigational formulation that combines the atypical antipsychotic Zyprexa(R) (olanzapine) with pamoic acid, allowing for the sustained delivery of olanzapine for up to four weeks.

Results from a 190-week interim analysis of a six-year, ongoing, open-label study (HGKB), showed that adults with schizophrenia or schizoaffective disorder treated with olanzapine LAI had a discontinuation rate of 46.3 percent. The most common reason for discontinuation was the patient's decision (23.4 percent) followed by adverse events (6.7 percent). Safety findings were consistent with those observed with oral olanzapine, with the exception of injection-related events, including post-injection delirium/sedation syndrome (PDSS), which is characterized by sedation- and/or delirium-related symptoms following injection.

"Discontinuation of medication plays a major role in schizophrenia relapse," said Holland Detke, Ph.D., clinical research scientist at Lilly. "Four out of five patients who stop taking their medications after a first episode of schizophrenia will have a relapse. The more relapses a patient has, the more difficult it becomes for them to recover from each successive relapse."(1)

Also presented today were eight-month interim results from a two-year, ongoing, open label study (HGLQ) that showed patients with schizophrenia could be switched to olanzapine LAI from a previous antipsychotic, either using a direct switch or while tapering their previous antipsychotic medication. No significant difference was found in overall rate of treatment discontinuation or mean change in PANSS score, two standard measures of treatment effectiveness in schizophrenia, among patients who were switched directly to olanzapine LAI and those who were tapered. Additionally, no significant differences were seen in the overall number of treatment-emergent adverse events, changes in laboratory measures or mean weight change.

Regulatory reviews for olanzapine LAI are ongoing in the United States and other countries. Olanzapine LAI is approved in the European Union under the brand name Zypadhera(R) for maintenance treatment of adults with schizophrenia who have been sufficiently stabilized during acute treatment with oral olanzapine.

Additional olanzapine LAI data presented today at the annual meeting of the American Psychiatric Association include: an analysis of the role of oral supplementation in the administration of long-acting antipsychotics; an analysis of PDSS; and a meta-analysis of olanzapine LAI, olanzapine and haloperidol data. Additionally, a cost-effectiveness simulation analysis comparing olanzapine LAI to risperidone LAI, haloperidol LAI and oral olanzapine was presented.

About HGKB

The primary objective of this ongoing open-label study is to examine the long-term safety and tolerability of olanzapine LAI. Current results are from an interim analysis, with maximum treatment duration of 190 weeks. Adult patients with schizophrenia or schizoaffective disorder (N=931) were enrolled following one of three randomized, controlled studies of olanzapine LAI, in which patients had been randomly assigned to oral olanzapine, olanzapine LAI or placebo. During the open-label extension, all patients received flexibly-dosed olanzapine LAI at injection intervals of approximately two to four weeks.

At time of analysis, rate of study discontinuation was 46.3 percent. Discontinuation rate at 18 months was 34.3 percent. The most common reasons for discontinuation were patient's decision (23.4 percent), followed by adverse events (6.7 percent). Adverse events in greater than or equal to five percent of patients were increased weight, insomnia, anxiety, somnolence, headache and inflammation of the nasal passages and upper pharynx (nasopharyngitis).

Safety findings were consistent with those observed with oral olanzapine, with the exception of injection related events, including PDSS. There were 26 occurrences of PDSS. All of these patients recovered within 72 hours. Mean weight change was +1.88 kg, with 32.1 percent of patients experiencing greater than or equal to seven percent weight gain. Percentages of patients who increased from normal to high on fasting glucose, random total cholesterol, or random triglycerides were 5.5 percent, 5.2 percent and 14.3 percent, respectively. Mean Clinical Global Impressions-Severity scores remained stable

throughout (2.9 at baseline to 2.8 at endpoint).

About HGLQ

The primary objective of this two-year, ongoing open-label study is to compare the treatment effectiveness of the oral and long-acting formulations of olanzapine in adult outpatients with schizophrenia considered at risk for relapse. The eight-month interim analysis of this study was conducted in order to compare the safety and effectiveness of direct switch versus taper of previous antipsychotic medication when changing to olanzapine LAI. Analyses were based on eight-month data from only those patients treated with olanzapine LAI (N=264). Patients received olanzapine LAI every four weeks with a starting dose of 405 mg and flexible dosing thereafter. Investigators, at their discretion, could either directly switch patients or taper their previous antipsychotic medication during the first two weeks of treatment.

At the time of study entry, patients were either receiving typical antipsychotics (N=63), atypical antipsychotics (N=188) or not receiving any antipsychotics at all (N=34). Of those receiving atypical antipsychotics, 76 were taking oral olanzapine and 16 were on an injectable antipsychotic medication other than olanzapine LAI.

Of 264 total patients, 150 (56.8 percent) were switched directly and the rest were tapered. The two groups did not significantly differ in discontinuation rate (direct: 29.3 percent, taper: 28.9 percent), and there was no significant difference between the groups on PANSS total score mean change at any visit up to eight months (direct: -1.5, taper: -3.4, from a mean baseline of 56.7).

Treatment-emergent adverse events in greater than or equal to five percent of patients were: increased weight (10.2 percent), insomnia (8.3 percent), anxiety (6.8 percent), somnolence (6.8 percent) and increased appetite (5.7 percent). The switch groups did not significantly differ in mean weight change, with an average weight gain of 2.0 kg, nor did they significantly differ in terms of laboratory analytes.

About PDSS

PDSS describes a range of signs and symptoms similar to those observed with oral olanzapine overdose that have been seen in 0.07 percent of olanzapine LAI injections in clinical trials as of February 22, 2009. These signs/symptoms include: sedation (ranging from mild in severity to unconsciousness) and/or delirium (including confusion, disorientation, agitation, anxiety or other cognitive impairment).

Other symptoms can include extrapyramidal symptoms (such as restlessness, muscle stiffness, random movements and tremors), difficulty articulating words (dysarthria), loss of coordination (ataxia), aggression, dizziness, weakness, hypertension and convulsions. As of February 22, 2009, across all clinical trials, PDSS events have been seen in approximately 2 percent of patients, all of whom have recovered. The majority of these patients have chosen to continue treatment with olanzapine LAI. Lilly has proposed a comprehensive plan to the FDA in order to help ensure the appropriate identification and management of PDSS.

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.(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.

Safety information for Oral Zyprexa (olanzapine)

Zyprexa is indicated in adults in the United States for the acute- and maintenance treatment of schizophrenia, acute mixed and

manic episodes of bipolar I disorder, and maintenance treatment of bipolar disorder.

Zyprexa is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

In addition, compared to elderly patients with dementia-related psychosis taking a placebo, there was a significantly higher incidence of cerebrovascular adverse events in elderly patients with dementia-related psychosis treated with Zyprexa.

The possibility of a suicide attempt is inherent in schizophrenia and bipolar I disorder. Close supervision of high-risk patient should accompany drug therapy.

As with all antipsychotic medications, a rare and potentially fatal condition known as Neuroleptic Malignant Syndrome (NMS) has been reported with Zyprexa. 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.

Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics, including Zyprexa. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and Zyprexa appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing Zyprexa to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level. Patients taking Zyprexa should be monitored regularly for worsening of glucose control. Patients starting treatment with Zyprexa should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, palyphagia and weakness. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Undesirable alterations in lipids have been observed with Zyprexa use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using Zyprexa, is advised. Significant, and sometimes very high, elevations in triglyceride levels and modest mean elevations in total cholesterol have been observed with Zyprexa use.

Potential consequences of weight gain should be considered prior to starting Zyprexa. Patients receiving Zyprexa should receive regular monitoring of weight.

As with all antipsychotic treatment, prescribing should be consistent with the need to minimize Tardive Dyskinesia (TD). The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Zyprexa 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 diseases, or those predisposed to hypotension.

Other potentially serious adverse events include seizures, elevated prolactin levels, elevated liver enzymes, cognitive and motor impairment, body temperature elevation and trouble swallowing.

The most common treatment-emergent adverse event associated with Zyprexa use in adults in placebo-controlled, short-term schizophrenia and bipolar mania trials was somnolence. Other common events were dizziness, weight gain, personality disorder (COSTART term for nonaggressive objectionable behavior), constipation, akathisia, postural hypotension, dry mouth, asthenia, dyspepsia, increased appetite and tremor.

Full prescribing information, including boxed warning, is available at www.zyprexa.com.

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.com.

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. "Expert Consensus Guideline Series," J Clin Psychiatry, 1999:60 (suppl 11).
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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