



## FDA Issues a Complete Response Letter for Lilly's Olanzapine LAI for Treatment of Schizophrenia in Adults

INDIANAPOLIS, Jan 07, 2009 /PRNewswire-FirstCall via COMTEX News Network/ --

Eli Lilly and Company (NYSE: LLY) announced today that it received a complete response letter from the U.S. Food and Drug Administration (FDA) for olanzapine long-acting injection (LAI) for acute and maintenance treatment of schizophrenia in adults. Lilly is continuing to work with the agency on the new drug application (NDA).

The FDA does not require any additional clinical trials for the continued review of the NDA. Per the agency's request, Lilly is preparing a proposed Risk Evaluation and Mitigation Strategy (REMS), which will be submitted in the near future.

"We cannot speculate on the timing of a potential decision, but remain confident that, if approved, the long-acting depot formulation of olanzapine will offer an important option for treating this devastating and chronic illness," said Todd Durell, M.D., associate medical director for U.S. neuroscience for Lilly.

This treatment has been approved for use in the European Union and New Zealand under the trade name Zypadhera(TM). Independent regulatory reviews are ongoing in other countries.

Notes for editors:

### 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 if it is determined that a depot formulation is necessary to help with compliance.(1)

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.(2) 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.(3)

### About Schizophrenia

Schizophrenia is a severe and debilitating illness with such symptoms 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.(4) In addition to these symptoms, patients with schizophrenia are at greater risk for medical comorbidities than the general population.

### Safety information for Zyprexa

Zyprexa oral is indicated in the United States for the short- and long- term treatment of schizophrenia, acute mixed and manic episodes of bipolar I disorder, and maintenance treatment of bipolar disorder.

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

Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics, including olanzapine. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level. Patients taking olanzapine should be monitored regularly for worsening of glucose control. 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.

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

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

Olanzapine 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.

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

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 oral Zyprexa 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 a boxed warning, is available at [www.zyprexa.com](http://www.zyprexa.com).

#### About Eli Lilly and Company

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](http://www.lilly.com).

#### P-LLY

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) Falkai P., Wobrock T., Lieberman J., Glenthøj 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

2) 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.

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

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