FDA Approves Lilly's ZYPREXA(R) RELPREVV(TM) for Treatment of Schizophrenia in Adults

Long-acting injection provides therapeutic olanzapine exposure for up to four weeks

INDIANAPOLIS, Dec 14, 2009 /PRNewswire-FirstCall via COMTEX News Network/ -- The U.S. Food and Drug Administration (FDA) approved ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension for the treatment of schizophrenia in adults, Eli Lilly and Company (NYSE: LLY) announced today. ZYPREXA RELPREVV, a long-acting intramuscular injection, sustains the delivery of olanzapine for up to four weeks.

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.(i)

"Patients, families and communities often needlessly suffer the consequences of relapse when daily schizophrenia medications are not taken as prescribed," said John Kane, M.D., chairman, Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, N.Y. "ZYPREXA RELPREVV gives patients an additional treatment option that can help them maintain therapeutic drug levels for up to four weeks at a time."

Approximately 2.4 million Americans or about 1.1 percent of the adult population have schizophrenia.(ii) Schizophrenia is a brain disorder characterized by acute episodes of delusions (false beliefs that cannot be corrected by reason) and hallucinations (usually in the form of non-existent voices), as well as long-term impairments such as diminished emotion, general lack of interest and depressive signs and symptoms.(iii,iv)

Proper treatment for schizophrenia can relieve symptoms, prevent or delay relapse and break the "revolving door" cycle often associated with schizophrenia.(v,vi) Non-adherence to antipsychotic medications greatly increases the risk of relapse in patients with schizophrenia.(vii) By administering long-acting medications, psychiatrists know when patients have received their medication and can immediately detect non-adherence when a patient does not return for a scheduled injection.(viii)

"There is a growing recognition among psychiatrists in the United States that non-adherence to medication is an even greater barrier to care for patients with schizophrenia than was previously understood, and that long-acting treatments can play a beneficial role in helping patients maintain a stable treatment regimen," said John Hayes, M.D., vice president of Lilly Research Laboratories. "ZYPREXA RELPREVV provides a new mechanism for helping appropriate patients benefit from the well-characterized efficacy of olanzapine."

The FDA approval is based on a broad clinical data package involving 2,054 patients, in which ZYPREXA RELPREVV was found to be effective in controlling symptoms of schizophrenia, including hallucinations, delusions, apathy and social withdrawal. Efficacy was shown without the need for oral supplementation. Clinical data showed that ZYPREXA RELPREVV dosages (150, 210, 300 and 405 mg) provide therapeutic olanzapine exposure for two or four weeks depending on the dose.

ZYPREXA RELPREVV was found to have a similar safety profile as oral olanzapine, with the exception of injection-related events, including post-injection delirium/sedation syndrome (PDSS). PDSS events include a wide range of signs and symptoms of sedation, from mild in severity to coma, and/or delirium, including confusion, disorientation, agitation, anxiety or other cognitive impairment. As of November 30, 2009, across all clinical trials, PDSS events have occurred in < 0.1 percent of injections and approximately 2 percent of patients. The potential for onset of an event is greatest within the first hour after injection. The majority of cases have occurred within the first three hours after injection; however cases have occurred after three hours. All patients largely recovered within 72 hours, and the majority of these patients have chosen to continue treatment with ZYPREXA RELPREVV. Labeling for ZYPREXA RELPREVV includes a requirement for the patient to be observed at a healthcare facility with ready access to emergency response services for at least three hours following each injection and to be accompanied to his or her destination upon leaving the facility.

Lilly worked with the FDA to develop a Risk Evaluation and Mitigation Strategy (REMS), which includes a communication plan, a patient medication guide and a mandatory Patient Care Program, which restricts distribution of ZYPREXA RELPREVV to prescribers, healthcare facilities, pharmacy service providers and patients enrolled in the program. The goal of the Patient Care Program is to mitigate the risk of negative outcomes associated with ZYPREXA RELPREVV PDSS.

This treatment has been approved in the European Union under the trade name Zypadhera(TM) and in New Zealand and Australia under the trade name ZYPREXA RELPREVV.

Safety Information for ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension

ZYPREXA RELPREVVis indicated in the United States for the treatment of schizophrenia in adults.

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

Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of ZYPREXA RELPREVV. ZYPREXA RELPREVV must be administered in a registered healthcare facility with ready access to emergency response services. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least three hours. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment.

Olanzapine 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 (e.g., transient ischemic attack) in elderly patients with dementia-related psychosis treated with olanzapine.

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.

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. Patients starting treatment with olanzapine 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 olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised. Clinically significant, and sometimes very high, elevations in triglyceride levels and modest mean elevations in total cholesterol have been observed with olanzapine use.

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

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.

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.

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

Other potentially serious adverse events include decreased white blood cell count (leukopenia, neutropenia, agranulocytosis), seizures, elevated prolactin levels, cognitive and motor impairment, body temperature elevation, and trouble swallowing.

The most common treatment-emergent adverse events (>5% in at least one of the ZYPREXA RELPREVVtreatment groups and greater than placebo) in the short-term, placebo-controlled trial were headache, sedation, weight gain, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite, and vomiting.

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 boxed warnings, is available at http://www.zyprexarelprevv.com.

About Lilly

Lilly, a leading innovation-driven corporation is developing a growing portfolio of 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.

Zyprexa(R) (olanzapine, Lilly)

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This press release contains forward-looking statements about ZYPREXA RELPREVV. These statements reflect management's current beliefs; however, as with any pharmaceutical product there are risks and uncertainties in the process of research and development, regulatory review and commercialization. There is no guarantee that ZYPREXA RELPREVV will be commercially successful in this indication. 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) Maxine X. Patel and Anthony S. David. (2005). Why aren't depot antipsychotics prescribed more often and what can be done about it? Advances in Psychiatric Treatment. 11: 203-211

(ii) Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK. (1993). The de facto mental and addictive disorders service system. Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Archives of General Psychiatry. Feb;50(2):85-94

(iii) Weiden P, Scheifler P, Diamond R, et al. (1999). *Breakthroughs in Antipsychotic Medications*. New York: W.W. Norton & Company

(iv) For a list of symptoms and complete diagnostic criteria for schizophrenia, see the Diagnostic and Statistical Manual of Mental Disorders, Ed 4, Text Revision (American Psychiatric Association; 2000)

(v) "Expert Consensus Guideline Series. (1999).*J Clin Psychiatry*.60 (suppl 11)

(vi) "The World Health Report 2001: Mental Health - New Understanding, New Hope," Chapter 3. World Health Organization. Available at http://www.who.int/whr/2001/chapter3/en/index1.html

(vii) Lacro JP, Dunn LB, Dolder CR, et al. (2002). Prevalence of and risk factors for medication non-adherence in patients with schizophrenia: a comprehensive review of recent literature. J Clin Psychiatry.63: 892 -909

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

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