FDA Approves Lilly's Zyprexa for Two Adolescent Indications

INDIANAPOLIS, Dec 04, 2009 /PRNewswire-FirstCall via COMTEX News Network/ -- The U.S. Food and Drug Administration (FDA) today approved Zyprexa(R) (olanzapine) in tablet form as an option for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents aged 13-17 years old.

The updated Zyprexa label states that clinicians should take into consideration the increased potential for weight gain and hyperlipidemia in adolescents compared to adults and the potential for long-term risks, which in many cases, may lead them to consider prescribing other drugs first in adolescents. Compared to patients from adult clinical trials, adolescents were also likely to experience increased sedation and greater increases in prolactin levels and hepatic transaminase (liver enzymes) levels. The recommended starting dose for adolescents is lower than that for adults.

An FDA Psychopharmacologic Drug Advisory Committee (PDAC) met in June and discussed the difficulties of diagnosing and treating these conditions in adolescents. The Zyprexa label provides additional guidance to physicians that medication therapy for pediatric schizophrenia or bipolar I disorder should be initiated only after a thorough diagnostic evaluation and careful consideration of the risks associated with medication treatment.

The updated Zyprexa label also highlights the need for a comprehensive treatment program in pediatric patients and recommends that Zyprexa be used as part of a "total treatment program for pediatric patients with schizophrenia and bipolar I disorder," which may include psychological, educational and social interventions.

This approval follows a favorable vote regarding the safety and efficacy of Zyprexa from the FDA PDAC in June on Lilly's supplemental New Drug Applications for these indications. The Committee examined findings from two pivotal clinical trials: one six-week trial in adolescents with schizophrenia and one three-week trial in adolescents with manic or mixed episodes associated with bipolar I disorder, as well as extensive Zyprexa safety data relevant to adolescents.

"There has been a recognized need in the mental health community for additional guidance on treating teens diagnosed with these serious mental illnesses," said Cherri Miner, M.D., Lilly USA Neuroscience Senior Medical Director. "Customers have been asking for data from controlled studies in these populations, and now with this information added to our label, we can help physicians make informed treatment decisions."

About Schizophrenia in Adolescents

Schizophrenia affects about 1 percent of Americans.(1) A substantial portion of first psychotic breaks for schizophrenia occur in adolescence. It has been estimated that 39 percent of males and 23 percent of females with schizophrenia experience onset of the disease before the age of 19.(2) Studies have suggested that early-onset schizophrenia is associated with worse long-term outcomes compared to onset of illness in adulthood.(3)

About Bipolar Disorder in Adolescents

Bipolar disorder affects approximately 5.7 million American adults, or about 2.6 percent of the U.S. population age 18 and older, in a given year.(4) It has an estimated prevalence of 0.1 percent to 2 percent among adolescents.(5) Lifetime prevalence of bipolar I disorder in community samples has varied from 0.4 percent to 1.6 percent.(6) It has been estimated that 20 percent of all patients with bipolar disorder experience their first episode during adolescence, with the peak age of onset for this group of patients occurring between 15 and 19 years of age.(7) Early onset of bipolar disorder is associated with greater severity of illness and more functional impairment.(8)

Safety Information for Zyprexa (olanzapine)

Zyprexa 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.

Zyprexa is indicated for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. When deciding among alternative treatments available for adolescents, clinicians should consider the increased potential for weight gain and hyperlipidemia compared to adults. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead clinicians to consider prescribing other drugs

first in adolescents.

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. stroke, transient ischemic attack) in elderly patients with dementia-related psychosis treated with olanzapine.

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 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.

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 recommended starting dose for adolescents is lower than that for adults. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential for weight gain and hyperlipidemia compared to adults. Clinicians should consider the long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents. Medication treatment for adolescent schizophrenia and bipolar I disorder should be initiated only after a thorough diagnostic evaluation and careful consideration of the risks associated with medication treatment. Medication treatment for both adolescent schizophrenia and bipolar I disorder is indicated as part of a total treatment program that often includes psychological, educational and social interventions. Safety and effectiveness of olanzapine in patients <13 years of age have not been established.

The most common treatment-emergent adverse event associated with oral Zyprexa in placebo-controlled, short-term schizophrenia and bipolar mania trials in adults 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.

The most common treatment-emergent adverse events associated with oral olanzapine (vs placebo) in clinical trials of adolescents (13-17 years old) were sedation (44% vs 9%), weight increased (30% vs 6%), increased appetite (24% vs 6%), headache (17% vs 12%), fatigue (9% vs 4%), liver enzymes increased (8% vs 1%), dizziness (7% vs 2%), dry mouth (6% vs 0%), pain in extremity (5% vs 1%).

Full prescribing information, including boxed warning, and medication guide are available at www.zyprexa.com.

About Lilly

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Zyprexa(R) (olanzapine, Lilly)

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This press release contains forward-looking statements about Zyprexa. 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. 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) The National Institute of Mental Health. What is Schizophrenia? Available at: http://www.nimh.nih.gov/health/publications/schizophrenia/what-is-schizophrenia.shtml. Accessed November 20, 2009.

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(5) Mauricio Tohen et al. (2007). Olanzapine versus Placebo in the Treatment of Adolescents with Bipolar Mania. *American Journal of Psychiatry*, 164: 1547-1556.

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