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4 January 2010

Re: Important Safety Information on ZYPREXA® (olanzapine) and Use in Adolescents

Dear Healthcare Professional,

We would like to inform you of the recent FDA approval of the use of oral ZYPREXA® (olanzapine) in adolescents (ages 13-17). Pertinent information from the Indications and Usage section (section 1) and Patient Counseling Information (section 17) of the US product label are shown below in italicized text:

> *Section 1.1, Schizophrenia: Oral ZYPREXA is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial.*
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> *When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents.*
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> *Section 1.2, Bipolar I Disorder (Manic or Mixed Episodes):*
> *Monotherapy — Oral ZYPREXA is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial.*
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> *When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents.*
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> *Section 1.3, Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder: Pediatric schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles*

can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

Section 17.13, Use in Specific Populations, Pediatric Use: ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. 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. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <18 years of age have not been established.

Section 17.14, Need for Comprehensive Treatment Program in Pediatric Patients: ZYPREXA is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of ZYPREXA have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

The recommended starting dose in adolescents is lower than that in adults. Although no studies were conducted comparing adolescent and adult patients, safety information from adolescent studies was compared to safety information from adult studies. The types of adverse events observed in adolescents were similar to those seen in adult patients. However, the magnitude and frequency of some events were greater in adolescents than in adults. Compared to patients from adult clinical trials, adolescents were likely to gain more weight and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels, and sedation. Prescribers should review the following safety information and the enclosed full prescribing information and Medication Guide and carefully consider the individual risk-benefit assessment for each adolescent.

Hyperglycemia:
Increases in fasting glucose were similar in adolescents and adults treated with olanzapine; however, the difference between olanzapine and placebo groups was greater in adolescents compared to adults.

In adolescents, as in adults, 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 levels (fasting 100-126 mg/dL, non-fasting 140-200 mg/dL). 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, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperlipidemia:
In adolescents, as in adults, undesirable alterations in lipids have been observed with olanzapine use. Clinically significant, and sometimes very high (>500 mg/dL) elevations in triglyceride levels have been observed with olanzapine use. Modest increases in total cholesterol have also been seen.

Increases in fasting total cholesterol, LDL cholesterol, and triglycerides were generally greater in adolescents than in adults treated with olanzapine.

Clinical monitoring, including baseline and periodic follow-up lipid evaluations is recommended.

Weight Gain:
As in adults, potential consequences of weight gain should be considered prior to starting olanzapine in adolescents. Patients receiving olanzapine should have their weight monitored regularly.

In olanzapine-treated adolescent patients, both the magnitude of weight gain and the proportion of patients who had clinically significant weight gain were greater than in adult patients with comparable exposures. The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure (≥24 weeks) were 89%, 55%, and 29%, respectively. Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated adolescent patients following at least 24 weeks of exposure.

Hyperprolactinemia:
Adolescents treated with olanzapine had a higher incidence of elevated prolactin levels compared with adults. There was also a greater incidence of galactorrhea and gynecomastia in adolescents compared to adults.

Sedation:
Sedation-related adverse events (defined as hypersomnia, lethargy, sedation, and somnolence) occurred at higher frequencies in adolescents compared to adults.

Because olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely.

Hepatic Transaminase Levels:
Compared to adult patients in clinical trials, adolescents were more likely to have greater increases in hepatic transaminases.

In adolescents, as in adults, caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Please refer to the Important Safety Information, full prescribing information, and the Medication Guide for ZYPREXA included with this letter. Should you have any questions, or if you would like additional information or educational materials regarding this important safety information, please contact the Lilly medical department at 1-800-Lilly-Rx or your Lilly sales representative.

The medical community can further our understanding of adverse events by reporting all events to the Food and Drug Administration via the MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, via the MedWatch website at: www.fda.gov/Safety/MedWatch, or by mail:

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Sincerely,

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