Standby Statement: Approved STB ID: 04-35

Date: March 17, 2004

Author: Marni Lemons

Issue: Zyprexa "Dear Doctor" Letter on Hyperglycemia and Diabetes

Background and Basic facts: On September 15, 2003, Lilly received a letter from the U.S. Food and Drug Administration (FDA) requesting updated product labeling for all atypical antipsychotics, to include a warning about additional information on hyperglycemia and diabetes. In addition to Zyprexa® (olanzapine), the atypical antipsychotic class includes Clozaril® (clozapine, Novartis), Risperdal® (risperidone, Janssen), Seroquel® (quetiapine, AstraZeneca), Geodon® (ziprasidone, Pfizer), and Abilify® (aripiprazole, Bristol Myers Squibb).

In the letter, the FDA recognized that the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood, but epidemiological studies have suggested some increased risk. The Agency's letter stated,

> "While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described, we believe the safe use of Zyprexa can be enhanced by informing prescribers and patients about these events. Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus may reduce the risk for the most serious outcomes," the FDA stated in its letter

The FDA letter requested a change in labeling be made so as to furnish adequate information for the safe and effective use of [Zyprexa], specifically stating,

> "Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population."

The labeling further states that patients with diabetes who begin taking atypical antipsychotics should be monitored for a worsening of glucose control, and those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting glucose testing at baseline, and periodically throughout treatment. Any patient developing suggestive symptoms during treatment with an atypical antipsychotic should be tested for diabetes.

Lilly proactively issued a press release on September 17, 2003, announcing the receipt of the labeling letter from the FDA, and restating the company's commitment to ongoing research and providing resources and information in the interest of the "complete wellness" of patients with severe and persistent mental illness. Furthermore, Lilly made the FDA letter available to physicians, news media and others who requested it.

Lilly complied with the FDA's requested and changed its labeling to add the FDA's requested language on hyperglycemia and diabetes on September 18, 2003. Slight revisions to the language were incorporated in the label with Zyprexa's Bipolar Maintenance approval on January 14, 2004. Lilly also submitted a proposed "Dear Doctor" letter to be sent to healthcare professionals, informing them of the FDA-mandated class labeling for atypical antipsychotics and hyperglycemia and diabetes. The FDA has now approved of that letter and it is scheduled to be sent to primary care physicians and psychiatrists throughout the United States on March 18, 2004.

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Key Messages:

- Lilly agrees with the FDA that the risk for diabetes among patients with severe mental illness should be considered and monitored by physicians regardless of which medication the patients are taking.

- The "Dear Doctor" letter is part of Lilly's ongoing commitment to work very closely with the FDA and physicians to make them aware of both the risks and benefits of Zyprexa and our other medications.

- A great deal of research over the years has shown that patients with schizophrenia and bipolar disorder are at greater risk for many illnesses, including diabetes, regardless of their treatment.

- A substantial body of scientific evidence supports Zyprexa's overall efficacy and safety profile. Since its introduction over seven years ago, more than 14 million patients worldwide have taken this dependable and life-saving medication.

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Questions and Answers

Q1. What does the letter say? Can you give me a copy?

A1. Yes, I will be happy to e-mail (or fax) a copy of the letter to you.

The letter begins by informing the physician that the FDA has asked all manufacturers of atypical antipsychotic medications, including Lilly, to add a warning statement on hyperglycemia and diabetes. It lists all the manufacturers and the names of their respective medications. The letter then states the full warning, as stated in Zyprexa's label:

> **Hyperglycemia and Diabetes Mellitus**
> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Zyprexa. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.
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> Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics 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.

Finally, the letter states how to contact Lilly for more information.

Q2. Have other manufacturers of atypicals changed their labels? Have they sent out similar letters?

A2. Clozaril's label contained language on the issue before the FDA's class labeling letter. Risperdal and Seroquel have both changed their labeling,

inserting the language on hyperglycemia and diabetes. We are not aware of any other manufacturers who have complied with the FDA's letter.

We are aware that a letter regarding updates to Seroquel labeling has been distributed to doctors. For the other atypical antipsychotics, you might wish to check with the other individual companies.

Q3. To whom did Lilly send the letter?

A3. The letter was sent on Thursday, March 18, 2004, to primary care physicians and psychiatrists across the United States.

Q4. Does Zyprexa cause or contribute to a patient developing diabetes or high blood glucose levels?

A4. We don't believe so. The available data do not establish a causal link between antipsychotics and diabetes. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics.

Patients with schizophrenia and bipolar disorder are at greater risk for many illnesses, including diabetes. In fact, people with serious mental illness are at up to four times higher risk than the general population for diabetes. As a result, doctors should be regularly evaluating these patients for their risk of diabetes and monitoring for symptoms of hyperglycemia, regardless of their psychiatric treatment.

The FDA sent letters to <u>all</u> manufacturers of second-generation antipsychotics (SGAs) in September, 2003, requesting that a warning be placed on all these products' labeling on hyperglycemia (elevated blood glucose) and diabetes. The FDA's letter recognized that the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood, but epidemiological studies have suggested some increased risk.

The FDA based its September, 2003, labeling decision on an exhaustive, multi year review of all available data, including case reports, epidemiologic studies and clinical trial data. This class labeling includes the following language:

"Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies

suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available."

Q5. What steps does Lilly take to warn physicians about adverse events?

A5. This "Dear Doctor" letter is a specific example of the types of steps we take to warn physicians about adverse events.

We take any reports of adverse events very seriously and we work very closely with physicians to make them aware of both the risks and benefits of Zyprexa and our other medications; and we proactively report all adverse events and new research to the FDA.

Q6. Lilly acknowledges that weight gain is a common side effect of Zyprexa, and weight gain is a well-known risk factor for diabetes. Doesn't that indicate that Zyprexa could cause diabetes?

A6. It is important to note that weight gain leading to obesity is just one of several risk factors associated with diabetes. Others include older age, family history of diabetes, high blood pressure and elevated glucose at baseline. In addition, the Canadian Diabetes Association now lists severe mental illness as a risk factor for diabetes, as well.

The fact is, head-to-head clinical studies and epidemiology studies show no consistent or clinically significant difference in the risk of diabetes among patients treated with different atypical antipsychotics, despite differences in their respective weight gain profiles.

In an analysis ("TED" Study on Treatment-Emergent Diabetes – See MJL1STB 03-91: APA 2203 TED Standby) of clinical studies (most a year long, involving thousands of patients), elevated baseline random glucose levels and presence of multiple risk factors for diabetes were significantly more likely to predict treatment-emergent diabetes in patients than weight gain and antipsychotic drug assignment.

Q7. Do you anticipate that this letter will have an effect on Zyprexa sales?

A7. It is not Lilly's policy to speculate on future sales.

All of the information contained in this letter has previously been publicly reported in other sources (press releases, news media, etc.).

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