DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-520 – Symbyax (olanzapine/fluoxetine combination)
NDA 20-592 – Zyprexa (olanzapine) tablets
NDA 21-086 – Zyprexa Zydis (olanzapine) orally disintegrating tablets
NDA 21-253 – Zyprexa IntraMuscular (olanzapine for injection)

Eli Lilly and Company
Attention: Robin Wojcieszek, R.Ph.
Associate Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Ms. Wojcieszek:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Symbyax (olanzapine/fluoxetine combination), Zyprexa (olanzapine) tablets, Zyprexa Zydis (olanzapine) orally disintegrating tablets, and Zyprexa IntraMuscular (olanzapine for injection).

We also refer to your April 25, 2007 submission, containing a briefing document that summarizes results on weight gain, lipids, glucose dysregulation, and metabolic syndrome.

We have reviewed the data you have submitted thus far as well as the available literature, and we would like to request that you make the labeling changes listed below pertaining to the effect of olanzapine and Symbyax on body weight, lipids, and glucose. We anticipate that additional labeling changes will be necessary when we have reviewed the results of the additional analyses that we have requested. Given that your completing these analyses and our review of them will take some time, we believe that it is in the best interest of the public health to make interim labeling changes now based on the data that we already have available.

We request that the following language regarding hyperglycemia be implemented in the WARNINGS subsection in place of the present language in labeling regarding this risk. In addition, we request the following language regarding weight gain and hyperlipidemia be added as new WARNINGS subsections: (strike through font denotes deletions to our labeling and double underline font denotes additions).

WARNINGS

~~**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 olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. 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.~~

~~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.~~

Hyperglycemia

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. 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. Olanzapine (and clozapine) treatments have been associated with a greater potential to induce hyperglycemia than other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The exposure adjusted mean increase from baseline to the average of the two highest serum concentrations of serum glucose was 13.7 mg/dl.

In another clinical trial database, where olanzapine and fluoxetine were administered individually and in combination in separate arms of the trial, a significantly higher number of patients who were normoglycemic (non-fasting blood glucose < 140 mg/dl) before treatment became hyperglycemic (non-fasting blood glucose > 200 mg/dl) at some point during the 6-12 weeks of treatment (olanzapine vs. placebo: 2.4% vs. 0.3% and olanzapine/fluoxetine combination vs. placebo: 2.9% vs. 0.3% placebo). Approximately one-third of patients on olanzapine (33.3%, n=27) and one-half of patients on the olanzapine/fluoxetine combination (45.7%, n=27) who had borderline increased serum blood glucose (non-fasting, between 140 and 200 mg/dl) at the beginning of the study progressed to high blood glucose (> 200 mg/dl) at some time during the 6-12 weeks olanzapine treatment.

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 (fasting 100 – 140 mg/dl, non-fasting 140 – 200 mg/dl). Patients taking olanzapine 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.

WARNINGS

Weight Gain

In placebo-controlled, 6-week studies, olanzapine-treated patients gained an average of 2.8 kg (6.2 lb), compared to an average 0.4 kg (0.9 lb) weight loss in placebo-treated patients; 29% of olanzapine-treated patients gained greater than 7% of their baseline weight, compared to 3% of placebo-treated patients. During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine-treated patients met the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 5.4 kg (11.9 lb).

Table 1 includes data on weight gain with olanzapine pooled from 68 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

Table 1. Weight Gain with Olanzapine Use

Amount Gained Kg (lb)	6 weeks (N=2,976) (%)	6 months (N=1536) (%)	12 months (N=778) (%)	24 months (N=422) (%)
≤0	27	21	20	22
0-5 (0-11 lb)	57	34	25	22
5-10 (11-22 lb)	15	26	25	22
10-15 (22-33 lb)	2	12	16	18
≥15 (>33 lb)	0	6	14	16

Adolescents — In pooled data from two placebo-controlled olanzapine monotherapy studies of adolescent patients with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), weight gain was reported as an adverse event in 29.6% of olanzapine-treated patients compared to 5.6% of placebo-treated patients. Olanzapine-treated patients gained an average of 3.9 kg, compared to an average of 0.2 kg in placebo-treated patients; 43.5% of olanzapine-treated patients gained greater than 7% of their baseline body weight, compared to 6.8% of placebo-treated patients. A categorization of patients by baseline on the basis of body mass index (BMI) revealed a similar mean increase in weight in the olanzapine-treated patients in each category. During long-term continuation therapy with olanzapine, 65% of olanzapine-treated patients met

the criterion for having gained greater than 7% of their baseline weight. Average weight gain during long-term therapy was 7.3 kg.

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

WARNINGS

Hyperlipidemia

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. In clinical trials among olanzapine-treated patients with random triglyceride levels of <150 mg/dL at baseline (N=659), 0.5% of patients experienced triglyceride levels of ≥500 mg/dL some time during the trials. [Note to sponsor: Insert placebo data here.] In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in fasting triglycerides in patients taking olanzapine was 40.5 mg/dL.

Modest mean increases in total cholesterol and decreases in HDL cholesterol have also been seen with olanzapine use. In phase 1 of CATIE, the median increase in fasting total cholesterol was 9.4 mg/dL.

Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised.

We request that you make these labeling changes within 30 days of this letter. In addition, we are requesting that you issue a "Dear Healthcare Practitioner" letter conveying this new prescribing information pertaining to the metabolic effects of olanzapine and Symbyax. Please submit this "Dear Health Care Practitioner" letter to us for review prior to distributing it.

We request that you include as the last paragraph of the "Dear Healthcare Practitioner" letter the following language:

> The Medical Community can further our understanding of adverse events by reporting all cases to the Agency 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/medwatch, or by mail:
>
> MEDWATCH
> Food and Drug Administration
> 5515 Security Lane
> Suite 5100, HFD-001
> Rockville, MD 20852

If you have any questions, call Sonny Saini, Pharm.D., Safety Regulatory Project Manager, at 301-796-0532.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
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