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Indianapolis, Indiana 46285
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October 5, 2007

**Re: Safety data on Zyprexa® (olanzapine) and Symbyax® (olanzapine and fluoxetine HCl capsules) – Hyperglycemia, Weight Gain, and Hyperlipidemia**

Dear Health Care Professional,

Eli Lilly and Company would like to inform you of important information being added to the Zyprexa® (olanzapine) and Symbyax® (olanzapine and fluoxetine HCl) labels. These labeling updates include new WARNINGS for Weight Gain and Hyperlipidemia and updated information in the WARNING for Hyperglycemia. These changes reflect results of recently completed pooled analyses of clinical trials in adults and adolescents as well as information from two published large studies of atypical antipsychotics, CATIE[1] and CAFE[2].

The new labeling language is detailed below. Monitoring of glucose, weight, and lipids is recommended during olanzapine and olanzapine/fluoxetine combination treatment. Guidelines published by the American Diabetes Association (ADA) following the consensus development conference[3] provide recommendations for the monitoring of blood glucose, weight, and lipid levels in those treated with atypical antipsychotics. Other highlights of the updated labeling include:

- Abnormal or borderline glucose levels at baseline are an important risk factor for further glucose increase.
- 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.
- Significantly greater mean increases in total cholesterol, LDL cholesterol, and triglycerides were observed in Zyprexa-treated patients compared with placebo-treated patients both with and without evidence of dyslipidemia at baseline.
- Labeling provides information on magnitude and distribution of weight gain over a two year period in Zyprexa-treated patients.
- Labeling also provides information on glucose, weight gain, and lipids from studies of Zyprexa for adolescent patients. Please note that Zyprexa and Symbyax are not approved currently for use in children and adolescents aged less than 18 years old.

Eli Lilly and Company remains committed to providing you with the most current product information available for the management of your patients and we will continue our ongoing research and analyses in these areas.

Please refer to the full prescribing information for Zyprexa and Symbyax included with this letter.

Should you have any questions or would like additional information regarding this important safety information, please contact the Lilly medical department at 1-800-Lilly-Rx or your Eli Lilly and Company sales representative.

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

Sincerely,

Tim Garnett, M.D.
Vice President,
Global Patient Safety
Eli Lilly and Company

**The following are the updated Hyperglycemia WARNINGS and the new Hyperlipidemia and Weight WARNINGS included in the Zyprexa label.**

## WARNINGS:

### Zyprexa:

The following is updated language in the WARNINGS section of the Zyprexa package insert, and will be reflected in other materials.

**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. 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. 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.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dl.

*Olanzapine Monotherapy in Adults* — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse events, patients treated with antidiabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). These patients had a statistically significantly greater mean increase in $HbA_{1c}$ compared to placebo. In patients with baseline normal fasting glucose levels (<100 mg/dL), 2.2% (N= 543) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 3.4% (N= 293) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 17.4% (N=178) of those treated with

olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 11.5% (N=96) of those treated with placebo.

*Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

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 100–126 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.

**Hyperlipidemia** — 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.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

*Olanzapine Monotherapy in Adults* — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL,

4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, or patients with high baseline lipid levels. Table 1 shows categorical changes in fasting lipid values.

**Table 1. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks**

| Laboratory Analyte | Category Change from Baseline | Treatment Arm | N | Patients |
|---|---|---|---|---|
| | | | | |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 745 | 39.6%[a] |
| | | Placebo | 402 | 26.1% |
| | Normal to High (<150 mg/dL to ≥200 mg/dL) | Olanzapine | 457 | 9.2%[a] |
| | | Placebo | 251 | 4.4% |
| | Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 135 | 39.3%[a] |
| | | Placebo | 65 | 20.0% |
| | | | | |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 745 | 21.6%[a] |
| | | Placebo | 402 | 9.5% |
| | Normal to High (<200 mg/dL to ≥240 mg/dL) | Olanzapine | 392 | 2.8% |
| | | Placebo | 207 | 2.4% |
| | Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL) | Olanzapine | 222 | 23.0%[a] |
| | | Placebo | 112 | 12.5% |
| | | | | |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 536 | 23.7%[a] |
| | | Placebo | 304 | 14.1% |
| | Normal to High (<100 mg/dL to ≥160 mg/dL) | Olanzapine | 154 | 0% |
| | | Placebo | 82 | 1.2% |
| | Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL) | Olanzapine | 302 | 10.6% |
| | | Placebo | 173 | 8.1% |

[a] Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

*Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant

differences were observed between olanzapine-treated patients and placebo-treated patients. Table 2 shows categorical changes in fasting lipid values in adolescent patients.

**Table 2. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies**

| Laboratory Analyte | Category Change from Baseline | Treatment Arm | N | Patients |
|---|---|---|---|---|
| | | | | |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 138 | 37.0%[a] |
| | | Placebo | 66 | 15.2% |
| | Normal to High (<90 mg/dL to >130 mg/dL) | Olanzapine | 67 | 26.9% |
| | | Placebo | 28 | 10.7% |
| | Borderline to High (≥90 mg/dL and ≥130 mg/dL to >130 mg/dL) | Olanzapine | 37 | 59.5% |
| | | Placebo | 17 | 35.3% |
| | | | | |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 138 | 14.5%[a] |
| | | Placebo | 66 | 4.5% |
| | Normal to High (<170 mg/dL to ≥200 mg/dL) | Olanzapine | 87 | 6.9% |
| | | Placebo | 43 | 2.3% |
| | Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 36 | 38.9%[a] |
| | | Placebo | 13 | 7.7% |
| | | | | |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 137 | 17.5% |
| | | Placebo | 63 | 11.1% |
| | Normal to High (<110 mg/dL to ≥130 mg/dL) | Olanzapine | 98 | 5.1% |
| | | Placebo | 44 | 4.5% |
| | Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL) | Olanzapine | 29 | 48.3%[a] |
| | | Placebo | 9 | 0% |

[a] Statistically significant compared to placebo.

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

*Olanzapine Monotherapy in Adults* — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg, which was statistically significantly different compared to an average 0.3 kg weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, which was statistically significantly different compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, which was statistically significantly different compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass

Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in zero placebo-treated patients.

During long-term continuation therapy with olanzapine (238 median days of exposure), 56% of olanzapine 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.

Table 3 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 3. Weight Gain with Olanzapine Use**

| **Amount Gained** kg (lb) | **6 Weeks** (N=2976) (%) | **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 |

*Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

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 7.4 kg.

## Information for Patients:

**Hyperglycemia** — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

**Weight Gain** — Patients should be counseled that olanzapine is associated with weight gain. Patients should have their weight monitored regularly.

**The following are the updated Hyperglycemia WARNINGS and the new Hyperlipidemia and Weight WARNINGS included in the Symbyax label.**

## WARNINGS:

### Symbyax:

The following is updated language in the WARNINGS section of the Symbyax package insert, and will be reflected in other materials.

**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 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. 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.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase I of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the two highest serum concentrations was 15.0 mg/dL.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX was associated with a statistically significantly greater mean change in random glucose compared to placebo (8.65 mg/dL versus -3.86 mg/dL). In patients with baseline normal random glucose levels (<140 mg/dL), 2.3% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 0.3% of those treated with placebo. In patients with baseline borderline random glucose levels (≥140 mg/dL and <200 mg/dL), 34.1% of those treated with SYMBYAX were found to have high glucose levels (≥200 mg/dL) during SYMBYAX treatment and were statistically significantly different compared to 3.6% of those treated with placebo. The difference in mean changes between SYMBYAX and placebo was greater in patients with evidence of glucose dysregulation at baseline (including those patients diagnosed with diabetes mellitus or related adverse events, patients treated with anti-diabetic agents,

patients with a baseline random glucose level ≥200 mg/dL, or a baseline fasting glucose level ≥126 mg/dL). These patients had a greater mean increase in $HbA_{1c}$.

Controlled fasting glucose data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL vs 0.17 mg/dL).

*Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a statistically significantly greater mean change in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). In patients with baseline normal fasting glucose levels (<100 mg/dL), zero out of 124 (0%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus 1 out of 53 (1.9%) of those treated with placebo. In patients with baseline borderline fasting glucose levels (≥100 mg/dL and <126 mg/dL), 2 out of 14 (14.3%) of those treated with olanzapine were found to have high glucose levels (≥126 mg/dL) during olanzapine treatment versus zero out of 13 (0%) of those treated with placebo.

Physicians should consider the risks and benefits when prescribing SYMBYAX to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100–126 mg/dL, nonfasting 140–200 mg/dL). Patients taking SYMBYAX 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.

**Hyperlipidemia** — Undesirable alterations in lipids have been observed with SYMBYAX use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using SYMBYAX, is advised.

Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with SYMBYAX use. Significant increases in total cholesterol have also been seen with SYMBYAX use.

Controlled fasting lipid data is limited for SYMBYAX.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, with treatment duration up to 12 weeks, SYMBYAX-treated patients had an increase from baseline in mean random total cholesterol of 12.1 mg/dL compared to a statistically significantly different increase from baseline in mean random total cholesterol of 4.8 mg/dL for olanzapine-treated patients and a decrease in mean random total cholesterol of 5.5 mg/dL for placebo-treated patients. Table 3 shows categorical changes in nonfasting lipid values.

**Table 3. Changes in Nonfasting Lipids Values from Controlled Clinical Studies with Treatment Duration up to 12 Weeks**

| Laboratory Analyte | Category Change from Baseline | Treatment Arm | N | Patients (%) |
|---|---|---|---|---|
| | | | | |
| Nonfasting Triglycerides | Increase by ≥50 mg/dL | OFC | 174 | 67.8% |
| | | Olanzapine | 172 | 72.7% |
| | Normal to High (<150 mg/dL to ≥500 mg/dL) | OFC | 57 | 0% |
| | | Olanzapine | 58 | 0% |
| | Borderline to High (≥150 mg/dL and <500 mg/dL to ≥500 mg/dL) | OFC | 106 | 15.1% |
| | | Olanzapine | 103 | 8.7% |
| | | | | |
| Nonfasting Total Cholesterol | Increase by ≥40 mg/dL | OFC | 685 | 35%[a,b] |
| | | Olanzapine | 749 | 22.7% |
| | | Placebo | 390 | 9% |
| | Normal to High (<200 mg/dL to ≥240 mg/dL) | OFC | 256 | 8.2%[a,b] |
| | | Olanzapine | 279 | 2.9% |
| | | Placebo | 175 | 1.7% |
| | Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL) | OFC | 213 | 36.2%[a,b] |
| | | Olanzapine | 261 | 27.6% |
| | | Placebo | 111 | 9.9% |

[a] Statistically significant compared to olanzapine.

[b] Statistically significant compared to placebo.

Controlled fasting lipid data is limited for SYMBYAX; however, in an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had statistically significant increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in

patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse events, patients treated with lipid lowering agents, patients with high baseline lipid levels. Table 4 shows categorical changes in fasting lipid values.

**Table 4. Changes in Fasting Lipids Values from Adult Placebo-Controlled Olanzapine Monotherapy Studies with Treatment Duration up to 12 Weeks**

| Laboratory Analyte | Category Change from Baseline | Treatment Arm | N | Patients |
|---|---|---|---|---|
| | | | | |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 745 | 39.6%[a] |
| | | Placebo | 402 | 26.1% |
| | Normal to High (<150 mg/dL to ≥200 mg/dL) | Olanzapine | 457 | 9.2%[a] |
| | | Placebo | 251 | 4.4% |
| | Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 135 | 39.3%[a] |
| | | Placebo | 65 | 20.0% |
| | | | | |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 745 | 21.6%[a] |
| | | Placebo | 402 | 9.5% |
| | Normal to High (<200 mg/dL to ≥240 mg/dL) | Olanzapine | 392 | 2.8% |
| | | Placebo | 207 | 2.4% |
| | Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL) | Olanzapine | 222 | 23.0%[a] |
| | | Placebo | 112 | 12.5% |
| | | | | |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 536 | 23.7%[a] |
| | | Placebo | 304 | 14.1% |
| | Normal to High (<100 mg/dL to ≥160 mg/dL) | Olanzapine | 154 | 0% |
| | | Placebo | 82 | 1.2% |
| | Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL) | Olanzapine | 302 | 10.6% |
| | | Placebo | 173 | 8.1% |

[a] Statistically significant compared to placebo.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the median increase in total cholesterol was 9.4 mg/dL.

*Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), for fasting HDL cholesterol, no statistically significant differences were observed between olanzapine-treated patients and placebo-treated patients. Table 5 shows categorical changes in fasting lipid values in adolescent patients.

**Table 5. Changes in Fasting Lipids Values from Adolescent Placebo-Controlled Olanzapine Monotherapy Studies**

| Laboratory Analyte | Category Change from Baseline | Treatment Arm | N | Patients |
|---|---|---|---|---|
| | | | | |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 138 | 37.0%[a] |
| | | Placebo | 66 | 15.2% |
| | Normal to High (<90 mg/dL to ≥130 mg/dL) | Olanzapine | 67 | 26.9% |
| | | Placebo | 28 | 10.7% |
| | Borderline to High (≥90 mg/dL and <130 mg/dL to ≥130 mg/dL) | Olanzapine | 37 | 59.5% |
| | | Placebo | 17 | 35.3% |
| | | | | |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 138 | 14.5%[a] |
| | | Placebo | 66 | 4.5% |
| | Normal to High (<170 mg/dL to ≥200 mg/dL) | Olanzapine | 87 | 6.9% |
| | | Placebo | 43 | 2.3% |
| | Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 36 | 38.9%[a] |
| | | Placebo | 13 | 7.7% |
| | | | | |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 137 | 17.5% |
| | | Placebo | 63 | 11.1% |
| | Normal to High (<110 mg/dL to ≥130 mg/dL) | Olanzapine | 98 | 5.1% |
| | | Placebo | 44 | 4.5% |
| | Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL) | Olanzapine | 29 | 48.3%[a] |
| | | Placebo | 9 | 0% |

[a] Statistically significant compared to placebo.

**Weight Gain** — Potential consequences of weight gain should be considered prior to starting SYMBYAX. Patients receiving SYMBYAX should receive regular monitoring of weight.

In an analysis of 7 controlled clinical studies, 2 of which were placebo-controlled, the mean weight increase for SYMBYAX-treated patients was statistically significantly greater than placebo-treated (4 kg vs -0.3 kg). Twenty-two percent of SYMBYAX-treated patients gained at least 7% of their baseline weight, with a median exposure of 6 weeks. This was statistically significantly greater than in placebo-treated patients (1.8%). Approximately 3% of SYMBYAX-treated patients gained at least 15% of their baseline weight, with a median exposure of 8 weeks. This was statistically significantly greater than in placebo-treated patients (0%). Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 2.5% of SYMBYAX-treated patients and zero placebo-treated patients.

Table 6 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 6. Weight Gain with Olanzapine Use**

| Amount Gained kg (lb) | 6 Weeks (N=2976) (%) | 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 |

During long-term continuation therapy with olanzapine monotherapy (238 median days of exposure), 56% of olanzapine 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.

*Olanzapine Monotherapy in Adolescents* — The safety and efficacy of olanzapine and olanzapine and fluoxetine in combination have not been established in patients under the age of 18 years. In an analysis of 4 placebo-controlled olanzapine monotherapy studies of adolescent patients (ages 13 to 17 years), including those with schizophrenia (6 weeks) or bipolar disorder (manic or mixed episodes) (3 weeks), olanzapine-treated patients gained an average of 4.6 kg, which was statistically significantly different compared to an average of 0.3 kg in placebo-treated patients, with a median exposure of 3 weeks; 40.6% of olanzapine-treated patients gained at least 7% of their baseline body weight, which was statistically significantly different compared to 9.8% of placebo-treated patients, with a median exposure of 4 weeks; 7.1% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 2.7% of placebo-treated patients, with a median exposure of 19 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories, but mean changes in weight were greater in adolescents with BMI categories above normal at baseline. Discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to zero placebo-treated patients.

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 7.4 kg.

## Information for Patients:

**Hyperglycemia** — Patients should be advised of the potential risk of hyperglycemia-related adverse events. Patients should be monitored regularly for worsening of glucose control.

**Weight Gain** — Patients should be counseled that SYMBYAX is associated with weight gain. Patients should have their weight monitored regularly.

**References:**

1. Lieberman, JA, Stroup, TS, McEvoy, JP, S. Swartz, MS, Rosenheck, RA, Perkins, DO, Keefe, RSE, Davis, SM, Davis, CE, Lebowitz, BD, Severe, J, Hsiao, JK. 2005. Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. New Engl J Med 353(12): 1209-1223.

2. McEvoy, JP, Lieberman,JA, Perkins, DO, Hamer, RM, Gu, H, Lazarus, A, Sweitzer, D, Olexy, C, Weiden, P, Strakowski, SD. 2007. Efficacy and Tolerability of Olanzapine, Quetiapine, and Risperidone in the Treatment of Early Psychosis: A Randomized, Double-Blind 52-Week Comparison. Am J Psychiatry 164:1050–1060.

3. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for Study of Obesity. 2004. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. Diabetes Care 27: 596-601. http://care.diabetesjournals.org/cgi/content/full/27/2/596

*Zyprexa® (olanzapine) is indicated for the short-term and maintenance treatment of schizophrenia. Zyprexa is also indicated as monotherapy or in combination with lithium or valproate for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder and as maintenance treatment in bipolar disorder. Symbyax® (olanzapine and fluoxetine HCl capsules) is indicated for treatment of depressive episodes associated with bipolar disorder.*