May 9, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological
Drug Products, HFD-120
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

**SPECIAL SUPPLEMENT-
CHANGES BEING EFFECTED**

Re: NDA 20-592 - Zyprexa® (olanzapine)

Pursuant to provisions of 21 CFR§314.70(c)(2)(i), we are submitting revised package labeling for the referenced product.

The following changes have been made:

1)

In the **WARNINGS** section, inclusion of reference to reports of neuroleptic malignant syndrome with olanzapine.

This sentence now reads: "A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine."

This change is supported by Attachment I.

2)

In the **ADVERSE REACTIONS**, *Additional Findings Observed in Clinical Trials*, Laboratory Changes section, inclusion of data from the olanzapine clinical trial database with respect to random plasma glucose levels.

This section now reads: "In the olanzapine clinical trial database, as of September 30, 1999, 4577 olanzapine-treated patients (representing approximately 2255 patient-years exposure) and 445 placebo-treated patients who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140 mg/dL or lower were identified. Persistent random glucose levels ≥ 200 mg/dL (suggestive of possible diabetes) were observed in 0.8% of olanzapine-treated patients (placebo 0.7%). Transient (i.e., resolved while the patients remained on treatment) random glucose levels ≥ 200 mg/dL were found in 0.3% of olanzapine-treated patients (placebo 0.2%). Persistent random glucose levels ≥ 160 mg/dL but < 200 mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 1.0% of olanzapine-treated patients (placebo 1.1%). Transient random glucose levels ≥ 160 mg/dL but < 200 mg/dL were found in 1.0% of olanzapine-treated patients (placebo 0.4%)."

This change is supported by Attachment II.

3)

In the **ADVERSE REACTIONS**, *Postintroduction Reports* section, inclusion of "diabetic coma".

This section now reads: "Adverse events reported since market introduction which were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: diabetic coma and priapism."

This change is supported by Attachment III.

Enclosed are 12 copies of the revised labeling (identified as PV3390AMP) in final printed form (Attachment IV). The labeling is dated April 12, 2000. Effective immediately, we will be implementing this change.

Please call Dr. Michele Sharp at (317) 277-8382 or me at (317) 277-3799 if there are any questions. Thank you for your continued cooperation and assistance.

Sincerely,
ELI LILLY AND COMPANY

Gregory T. Brophy, Ph.D.
Director
U.S. Regulatory Affairs

ATTACHMENT I

As of September 30, 1999, an estimated 3,536,000 patients had been treated with olanzapine. As of this same date, 334 spontaneous adverse event reports referring to possible cases of Neuroleptic Malignant Syndrome (NMS) for olanzapine were received by Eli Lilly and Company. The reports were categorized with respect to whether or not they met criteria within the following diagnostic systems for NMS: APA/DSM-IV, McClean/Pope/Keck, and Caroff. A review of this data indicate that only one of the 334 reports definitely met accepted criteria for NMS that could be attributed to olanzapine. There were 38 cases which definitely did not meet inclusion criteria for NMS, therefore there were somewhere between 1 and 296 cases meeting criteria for NMS.

Based on these data, we have implemented the accompanying labeling change.

ATTACHMENT II

As of September 30, 1999, 5030 olanzapine-treated patients and 513 placebo patients with evaluable random gluocse measurements were identified in the olanzapine clinical trial database, which consisted of 78 different studies conducted by Eli Lilly and Company and completed for analysis. An analysis of this database was conducted by collecting non-fasting plasma glucose concentration data from all patients with any on-treatment value ≥ 160 mg/dL. Those olanzapine-treated patients who had a history of diabetes mellitus or hyperglycemia and whose baseline random plasma glucose levels were > 140 mg/dL were excluded from the analysis.

Patients with post-treatment glucose concentrations ≥ 160 mg/dL but < 200 mg/dL were categorized as having potential impaired glucose tolerance but not of diabetic magnitude, and those with glucose concentrations ≥ 200 mg/dL were categorized as having potential diabetes. These values were adapted from the American Diabetes Association guidelines for the use of random glucose in directing further evaluation of potential diabetes.

When reviewing the longitudinal patterns of random glucose values, the increased glucose values were categorized as persistent or transient. Persistent is defined as a glucose concentration elevated above threshold during treatment and at endpoint. The persistent category also included those uncertain cases where glucose concentration was elevated above threshold only at treatment endpoint. Transient referred to a glucose concentration elevated above threshold during some interval during treatment but clearly decreased by endpoint.

The following table provides the results from this analysis.

Table. Incidence of Treatment-emergent Potential Diabetes or Potential Hyperglycemia by Treatment

	Olanzapine		Placebo	
	N	Percent	N	Percent
Potential Diabetes (Persistent/Uncertain)	36	0.79	3	0.67
Potential Diabetes (Transient)	12	0.26	1	0.22
Potential Hyperglycemia (Persistent/Uncertain)	46	1.01	5	1.12
Potential Hyperglycemia (Transient)	47	1.03	2	0.44
Probable lab error	125	2.73	12	2.70
No Glycemic Problem	4311	94.19	422	94.83
Total	4577	100.00	445	100.00

Based on these data, we have implemented the accompanying labeling change.

ATTACHMENT III

As of September 30, 1999, an estimated 3,536,000 patients had been treated with olanzapine. As of this same date, 6 spontaneous adverse event reports mapped to the COSTART term of diabetic coma for olanzapine were received by Eli Lilly and Company. These 6 cases are identified as:

1. DE_981100634
2. US97021057A
3. US97091735A
4. US_981112856
5. US_990420242
6. US_990522556

One report (US_990420242) identified death as the outcome. All of these reports have previously been submitted to the Agency in a timely fashion.

Based on these data, we have implemented the accompanying labeling change.

ATTACHMENT IV

OLANZAPINE AND ASSOCIATED DIABETIC COMA IN THE SPONTANEOUS SAFETY DATABASE FROM 9/27/96 THROUGH 9/30/99 (1ST 3 years on market)

Overview: As of the datalock point for the fifth Periodic Safety Update Review (PSUR) which is September 30, 1999 there were only 6 spontaneous cases mapped to the COSTART term of Diabetic Coma. The worldwide patient exposure through September 30, 1999 was estimated to be 3,536,000. Therefore the reporting frequency was listed as (6 cases among 3.536 million patients) 0.00016% or considered to be "very rarely" reported as a description.

Cases: The 6 cases are displayed in table 1 with some general information. The mean age of the 6 patients is 43.2. The gender mix includes 4 males and 2 females among the 6 cases.

Table 1

#	CASE ID	AGE / SEX	COSTART TERM(s)	PEAK BS	CONFOUNDING/ RISK FACTORS	OUTCOME
1	DE_981100634	28 /male	Diabetic Coma, Hyperglycemia Diabetes Mellitus, Nausea, Abdominal Pain	800mg% with severe acidosis (pH=6.8)	None known	Unknown
2	US97021057A	40/ female	Diabetic Coma, Diabetes Mellitus, Diabetic Acidosis, NMS, Kidney Function Abnormal, Asthenia, Hypotension, Fever	1400 mg% (hyperosmolar coma)	Family history of diabetes. Patient was an undiagnosed diabetic at time of event: hemoglobin A1C was 12.3	Resolved and discharged on insulin therapy.
3	US97091735A	72/ male	Diabetic Coma, Hyperglycemia Thirst, Somnolence, Nervousness, Manic Reaction,	1700 mg%	Consumption of large quantities of malted beverages just prior to events	Resolved and hypoglycemic not used upon discharge.
4	US_981112856	33/ male	Diabetic Coma, Diabetes Mellitus, Acute Kidney Failure, Apnea	1676 mg% (hyperosmolar coma)	Morbid obesity, Hemoglobin A1C at time of event was 21.7	Recovered and placed on insulin.
5	US_990420242	45/ female	Diabetic Coma, Hyperglycemia Malaise, Polyuria, Thirst, Increased Appetite, Death	Unknown	Obesity, History of polydipsia, polyphagia and polyuria prior to start of olanzapine.	Death. Patient succumbed to complications of blood sugar elevation 4 days after admitted to hospital.
6	US_990522556	41/ male	Diabetic Coma, Hyperglycemia	1033 mg%	None known	Blood sugars remain difficult to control even with insulin therapy.

Potential other cases: The spontaneous safety database was also explored for cases with the COSTART term of Diabetic Acidosis. There were 35 cases found with this term. These cases were not examined for any cases of diabetic coma but some may be present.

BILL BROOKFIELD / Pharmacovigilance April 26, 2000