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February 6, 2004

Dr. Russell Katz, M.D., Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Woodmont Building, No. II
Attn: Document Division Room
1451 Rockville Pike
Rockville, MD 20852

RE: **Zyprexa (olanzapine): NDA 20–592/SLR-024 and NDA 21-086/SLR-007**

**FOR REVIEW AND COMMENT: Proposed Dear Health Care Professional Letter**

Dear Dr. Katz,

Reference is made to our supplemental new drug application dated September 18, 2003, which provided for a "Changes Being Effected" supplement for inclusion of information in labeling, under WARNINGS, regarding diabetes mellitus and hyperglycemia and to the Agency's letter dated December 16, 2003 informing Lilly that this supplement is approvable. This approvable letter requested additional changes to the labeling in addition to a request to issue a letter communicating this important labeling change. Reference is also made to the Agency's letter to NDA 20-592/S-019 which provided approval for the use of olanzapine in the maintenance treatment of bipolar I disorder and also included the revised wording for the WARNING, regarding diabetes mellitus and hyperglycemia as outlined in the December 16, 2003 Agency letter.

This submission provides for a proposed Dear Health Care Professional letter regarding the updated label change to include a WARNING regarding hyperglycemia and diabetes mellitus. A copy of this letter is attached.

We would like to request the Division to review the attached letter by February 13, 2004, and would also be available to discuss the letter by teleconference, if necessary.

We will submit a copy of the final Dear Health Care Professional letter to this NDA, MEDWATCH and the Division of Drug Marketing, Advertising, and Communications (DDMAC).

Please call me at (317) 277-8382 if you require any additional information or if there are any questions. Alternatively, you may contact Dr. Gregory T. Brophy, Ph.D., Director, U.S. Regulatory Affairs at (317) 277-3799. Thank you for your continued cooperation and assistance.

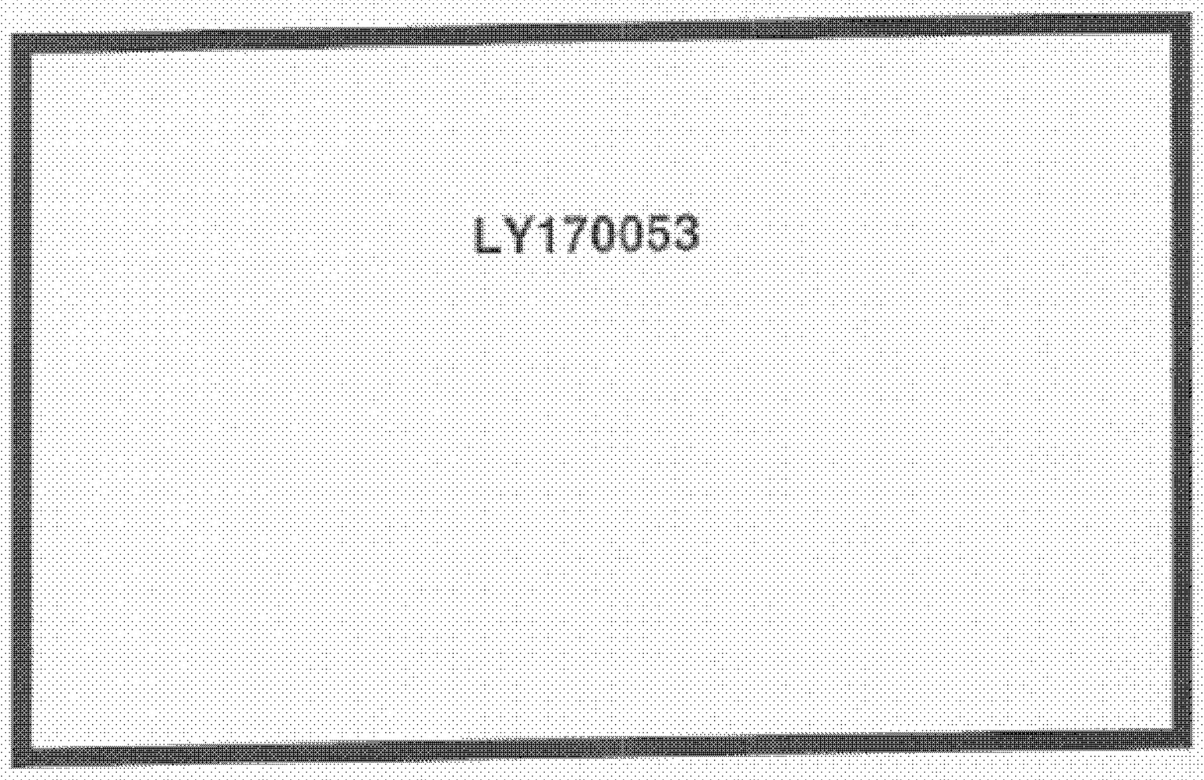
Sincerely,

ELI LILLY AND COMPANY

/s/

Michele Sharp, PharmD
Regulatory Research Scientist
U.S. Regulatory Affairs

Enclosure
Desk Copy: Steve Hardeman, R.Ph.



DATE

Re: Safety data on Zyprexa® (olanzapine) – Hyperglycemia and Diabetes

Dear Doctor,

Eli Lilly and Company would like to inform you of important labeling changes regarding Zyprexa (olanzapine). The FDA has asked all manufacturers of atypical antipsychotic medications, including Eli Lilly, to add a Warning statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications, including Zyprexa. In addition to Zyprexa, the atypical antipsychotic class includes Clozaril® (clozapine, Novartis), Risperdal® (risperidone, Janssen), Seroquel® (quetiapine, AstraZeneca), Geodon® (ziprasidone, Pfizer), and Abilify (aripiprazole, Bristol Myers Squibb and Otsuka American Pharmaceutical). Accordingly, the Zyprexa prescribing information has been updated with the following information:

**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. 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.

Should you have any questions or concerns regarding this important safety information, please contact your Eli Lilly and Company sales representative or contact the Lilly medical department at 1-800-Lilly-Rx. Please refer to the full prescribing information for Zyprexa included with this letter. As always, we request that serious adverse events be reported to Lilly at 1-800-Lilly-Rx or to the FDA MedWatch program by phone 1-800-FDA-1088, by fax (1-800-FDA-0178) or by email (www.fda.gov/medwatch).

Sincerely,

Dr. Paul Eisenberg
Vice President, Global Drug Safety
Eli Lilly and Company

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.

# Diabetes Label Change Journal Ad-

FOR INTERNAL USE ONLY. NOT FOR USE IN DETAILING

This communication is to notify all US field personnel responsible for Zyprexa that Lilly will begin running a journal ad highlighting the relationship between schizophrenia and diabetes consistent with the new label information from the FDA. This ad will help reinforce our dialogue with customers around counseling their patients about the risk of diabetes, and the 2- to 4-times greater risk of diabetes among persons with mental illness*. This journal ad will run for a 3-month period beginning in January 2004 in several professional publications including:

**Psychiatry**

AM JRL OF GERIATRIC PSYCHIATRY
AM JRL OF PSYCHIATRY
CLIN PSYCHIATRY NEWS
CNS NEWS
CURRENT PSYCHIATRY
JRL OF CLIN PSYCHIATRY
PRIMARY PSYCHIATRY
PSYCHIATRIC ANNUALS
PSYCHIATRIC NEWS
PSYCHIATRIC TIMES

**Psychiatric Nursing**

ARCH OF PSYCHIATRIC NURSING
JRL OF AM PSYCH NURSES ASSOC
JRL OF PSY NURSING & MH SERVICES

**Case Management**

CASE MANAGER
CARE MANAGEMENT

**Primary Care**

CONSULTANT
DIVERSION
FAM PRACTICE NEWS
INTERNAL MEDICINE NEWS
JRL OF AM MEDICAL ASSOC
MED ECONOMICS
MONTHLY PRESCRIBING REFERENCE
PATIENT CARE

The journal ad encourages readers to contact their Lilly sales representative for more information. Should your customers come to you with concerns about diabetes, you may use the following resources to respond to them:

- DVD: Breier Marketplace Update (OL28877)
- Zyprexa FDA Hyperglycemia Letter (OL29068)
- Diabetes Education Program- see separate attachment for a specific Request for Lecture Form
- 1-800-LILLY-RX for medical information

In response to an UNSOLICITED medical request:

- Medical Letter
- Medical Liaison (ML)

* Mukherjee S. et al. *Compr Psychiatry.* 1996; 37:68-73.