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Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285 U.S.A.

Phone 317 276 2000

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Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

SUPPLEMENT - CHANGES BEING EFFECTED

Re: NDA 20-592 - Zyprexa® (olanzapine) tablets
NDA 21-086 - Zyprexa® Zydis® (olanzapine) orally disintegrating tablets

Reference is made to FDA letter dated September 11, 2003 and received by Lilly on September 15, 2003 that provides for inclusion of a Warning regarding hyperglycemia and diabetes mellitus in product labeling.

In response to FDA request and pursuant to provisions of 21 CFR§314.70(c)(2)(i), we are submitting revised package labeling for the referenced product. As specified in the letter from FDA, we are including the following information under 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 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 studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.

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 baseline 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.

With this submission, we are providing PDF versions of approved labeling (PV 3399AMP) and current labeling in use (PV 3390AMP) and WORD and PDF versions of the mocked-up version incorporating the requested changes (PV 3391AMP).

Based on our communications, it is Lilly's understanding that this revised package labeling is being implemented identically for all atypical antipsychotics. If the revised class labeling is changed, then Lilly will work with the FDA to determine appropriate revisions.

Reference is also made to the following statement in the FDA's letter:

"Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available."

If new information becomes available with regard to antipsychotic use and diabetes mellitus adverse events, Lilly would like to continue to work with the FDA to discuss any additional class labeling changes that may be required.

This Changes Being Effected labeling supplement is submitted in electronic format according to the January 1999 "Guidance for Industry Providing Regulatory Submissions in Electronic Format – NDAs." This entire submission is provided in electronic format on CD Rom. The submission size is less than 5 megabytes. All electronic media have been checked by representatives of Lilly Information Technology and have been verified to be free of known viruses. The virus checking software was Norton AntiVirus Corporation Edition version 7.51.847 using Virus Definitions 50911Y created on September 11, 2003.

We have posted this version of the USPI (Version PV 3391AMP) to our website www.zyprexa.com. We would like to inform you that due to the lead times required to print and adhere the updated version of the USPI to packaged materials and the need to continue release of product, we will continue to release product with Version PV 3390AMP of the product label submitted to FDA on August 5, 2003 until the next production round is available. Based on our current estimates, this should be revised by

mid-October (approximately). When Version PV 3391AMP is available, we will destroy all current inventory of the previous label (PV 3390AMP).

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

Michele Sharp

Michele Sharp, Pharm. D.
Regulatory Research Scientist
U.S. Regulatory Affairs