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A Division of Eli Lilly and Company

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July 31, 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

RESPONSE TO FDA REQUEST

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

Enclosed is our response to your May 1, 2000 letter requesting information with olanzapine. To assist you in reviewing this information, the attached "Note to Reviewer" provides a description of how the response is organized.

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

cc: Mr. Steve Hardeman, RPh (3 copies)

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Note to Reviewer

As requested in your May 1, 2000 letter (received May 10, 2000), we are providing extensive safety information with olanzapine to assist you in fully evaluating the possibility that atypical antipsychotics may produce disturbances in glucose metabolism.

The data requested in your letter can be found in the attached document in the sections specified below:

“A comprehensive review of all preclinical data pertaining to hyperglycemia.”

Section 3 Olanzapine Review of Preclinical Data Pertaining to Hyperglycemia

“A thorough assessment of all Phase 1, 2, and 3 studies in the olanzapine NDA and any subsequent supplements for evidence of new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia. This should include the frequency of deaths, serious adverse events, total adverse events, and dropouts due to events related to abnormalities of glucose metabolism listed above, data regarding mean changes from baseline in plasma glucose level, and the percentage of patients meeting criteria for a markedly abnormal plasma glucose concentration from an appropriate pool of placebo-controlled Phase 2/3 studies. Any deaths, dropouts, or serious adverse events should have an accompanying detailed narrative summary.”

Section 4 Phase I Historical Data and

Section 5 Methods and Database Descriptions: Olanzapine Historical Glucose Analyses

“A review of spontaneous postmarketing reports for new-onset diabetes mellitus, hyperosmolar coma, diabetic ketoacidosis, weight gain, and hyperglycemia.”

Section 7 Spontaneous Case Report Review

“An estimate of patient exposure.”

Section 7 Spontaneous Case Report Review

“Copies of any correspondence with foreign regulatory agencies related to these events in association with olanzapine.”

Section 10 Appendix

“In addition, we ask that you investigate the possibility of collaborating with organizations having large pools of treated patients (e.g., HMO or VA databases) that

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might be examined for evidence of hyperglycemia or new-onset diabetes mellitus associated with olanzapine.”

Section 8 Ongoing Studies

In addition to the data that you requested, we are also providing a review of published literature (**Section 2, Literature Review**), an analysis of our clinical trial safety database as of September 30, 1999 (**Section 6, New Clinical Trial Analyses**) and a description of ongoing clinical studies (**Section 8, Ongoing Studies**).

The results from the analysis of our clinical trial safety database (**Section 6**) and review of our spontaneous case reports (**Section 7**) served as the basis for the safety labeling change submitted on May 9, 2000. The labeling change included:

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.

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

In conclusion, we believe that the results from this comprehensive review of olanzapine data completed in response to your May 1, 2000 letter are sufficiently conveyed in the labeling change submitted to FDA on May 9, 2000 and no additional labeling changes are warranted at this time.

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Hyperglycemia, Weight Gain, and Olanzapine

Eli Lilly and Company
(July 2000)

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Olanzapine (LY170053)

Hyperglycemia Regulatory Response

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