DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

NOV 14 1996

Charles R. Perry Jr.
Director
Pharmaceutical Communications and Compliance
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

RE: **NDA# 20-592**
Zyprexa (olanzapine)
MACMIS ID # 4682

Dear Mr. Perry:

This concerns a number of labeling pieces for Zyprexa identified as a multi-page detail aid, OL-0026; Stat-Grams identified as OL-0077 and OL-0078; a letter to the California Department of Health Sciences (assumed to be an example of similar letters to other states) with an attached backgrounder; and a "John Q. Public" letter, all submitted as required with a form FDA 2253 and also found during normal surveillance activities. This also concerns other promotional activities, such as, an interactive teleconference held on or about October 2, 1996. The Division of Drug Marketing, Advertising and Communications (DDMAC) considers these promotional labeling pieces, and promotional activities to be false or misleading, and in violation of the Federal Food, Drug, and Cosmetic Act (Act).

The promotional campaign, including the above identified labeling pieces and others submitted with the form 2253s, is lacking in appropriate balance, thereby creating a misleading message about Zyprexa. The promotional materials emphasize efficacy data but do not provide sufficient balance relating to adverse events and cautionary information. Further, they do not adequately or prominently discuss several important adverse events specifically selected for emphasis in the approved labeling. These events include orthostatic hypotension, seizures, transaminase elevations, weight gain, dizziness, and akathisia.

A. Specifically, the referenced detail aid, OL-0026, is in violation of the Act in the following particulars:

1. On page fifteen, in the summary of the Safety Profile for Zyprexa, several of the bulleted statements are considered to be misleading:

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a. "Avoids clinically significant changes in orthostatic blood pressure." This statement is misleading because the approved labeling includes a lengthy discussion of orthostatic hypotension, including syncope, caused by Zyprexa and suggests this event can be minimized by starting with a 5mg QD dose. In addition, Lilly has failed to provide information that dizziness occurs in 11% and postural hypotension occurs in 5% of patients.

b. "Transient, asymptomatic elevations in hepatic transaminases." This is misleading because the approved labeling states about 1% of patients discontinued treatment because of elevated transaminases, and states caution should be exercised in patients with hepatic impairment. While a footnote on this page mentions that periodic reassessment of transaminases is recommended in patients with hepatic disease, this footnote does not provide sufficient balance for this claim. The entire thrust of this campaign is to point out that Zyprexa is different and safer than older antipsychotic drugs. Therefore, it is necessary to properly emphasize those adverse events that do occur, that require caution when using Zyprexa.

2. On page three, the last bulleted statement reads, "Patients with intolerance to other antipsychotics because of extrapyramidal or other adverse reactions." This statement is misleading because it lacks proper balance and does not accurately reflect the information in the approved labeling. For example, the labeling reports a dose related increase in extrapyramidal symptoms, and tardive dyskinesia is listed as a Warning and as a frequent adverse event.

3. The subheadlines, "Outstanding control over the Combination...," "Outstanding Control of Positive Symptoms," and "Outstanding Control of Negative Symptoms" appear on pages four, six, and eight, respectively. These subheadlines are regarded as implications of superiority over other antipsychotic products that are unsubstantiated. While DDMAC does not question the efficacy of Zyprexa or its ability to "control symptoms," terms such as "outstanding" are usually interpreted as claims of superiority and, as such, must be adequately supported.

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4. On page twelve a discussion of adverse events appears. In the listing of other commonly observed adverse events, tardive dyskinesia is not included. The approved labeling lists tardive dyskinesia as both a Warning and as an adverse reaction occurring frequently, being defined as at least 1/100 patients (1%). It also minimizes the dose related increases in all extrapyramidal symptoms, e.g. 25% at 10mg., and 32% at 15mg. versus 16% for placebo.

5. On page 16, the bullet "No dosage adjustments for most elderly" is misleading. The approved labeling states that caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity. However, the bullet suggests that dosing is simple and easy and does not convey any cautionary information.

6. On page 19, the presentation of Zyprexa's pharmacologic profile is misleading. The labeling states that the mechanism of action is unknown and provides proposed theories of the drug's activities. However, Lilly has presented Zyprexa's activity as a fact and implies that there are less adverse events, such as extrapyramidal motor function, due to the selective action. However, a low incidence of extrapyramidal effects is not due to selective modulation of pathways implicated in schizophrenia.

   Further, Lilly has selectively chosen to present Zyprexa's more beneficial proposed actions and has not included, for example, that the drug antagonizes α-adrenergic receptors, thus explaining its orthostatic hypotension effects. In addition, the claim that Zyprexa is a selective modulator in the first three bullets is inconsistent with the claim in the last bullet that Zyprexa demonstrates broad pharmacologic activity.

   It should be emphasized that the pharmacological action of Zyprexa to alleviate psychotic symptoms is unknown.

The other labeling pieces identified above contain one or more of the violations enumerated above. They all are lacking in balance relating to adverse events and precautionary information, and present a misleading impression of Zyprexa as a superior, highly effective, virtually free of side effects, easy to use product. This impression is contrary to the approved labeling.

B. The Interactive Teleconference held on or about October 2, 1996, by Dr. Gary D. Tollefson, Vice President of Lilly Research Laboratories, is misleading in the following particulars:

1. Dr. Tollefson states that the therapeutic effects of Zyprexa are maintained over at least one year. The approved labeling states the effectiveness of the product was only established in short-term (six week) studies. Therefore, for any use over six weeks, the physician should periodically re-evaluate the long-term effectiveness of Zyprexa. However, this cautionary information for the indication is never presented in the teleconference.

2. The possibility of tardive dyskinesia, the fact that it is in the Warnings section and its incidence as a frequent adverse event, as discussed in the approved labeling, is minimized by Dr. Tollefson's statements, such as, "...we've been able to show that there is a statistically and significantly lower incidence of this neurological side effect with Zyprexa than with conventional drugs." Thus, Dr. Tollefson's statements are misleading because he does not go on to discuss the incidence of tardive dyskinesia, which is listed both as a Warening and as a frequent adverse reaction in the approved labeling, or discuss other extrapyramidal symptoms, such as akathisia, with Zyprexa. These symptoms have an extensive discussion in the approved labeling.

3. Dr. Tollefson states, "We are very pleased that the labeling in the U.S. will show by objective rating scales that both Parkinsons-like side effects and restlessness, or akathisia, the incidence across all doses of Zyprexa was comparable to placebo." This statement is misleading because the table in the approved labeling that lists adverse effects shows that the incidence of both Parkinsonian symptoms and akathisia increase well above placebo as the dosage increases.

4. Dr. Tollefson states that, "...Zyprexa is a unique molecule in that it is a compound with very, very low risk of drug/drug interactions. And this is something that will be featured, or highlighted in the labeling.". While the labeling states there is little risk of drug interactions, and few have been observed in clinical trials, the labeling cautions that coadministration of diazapam or ethanol with olanzapine potentiates orthostatic hypotension. This drug interaction precaution is not discussed, nor is orthostatic hypotension discussed, in any form during the presentation.

5. When asked a question about weight gain, Dr. Tollefson's response misleadingly turned an adverse event into a therapeutic benefit. He states, "So we went back and analyzed our data and saw that the vast majority of weight gain reported initially as an adverse event, in fact, was weight gain occurring in patients who had baseline before starting treatment, had been below their ideal body weight. **So we really look at this, with the majority of patients, as being part of a therapeutic recovery rather than an adverse event. And that data, I think is fairly compelling, because it was included in our labeling.** (Emphasis added)"

   The information on weight gain was indeed included in the approved labeling, but as an adverse event, not a therapeutic benefit. Since the product was approved at the time of this teleconference, Dr. Tollefson knew or should have known what information the approved labeling contained and in what section it appeared. His statements were therefore, false and misleading.

6. Dr. Tollefson states, "So the routine starting dose on day one will be ten milligrams." He made no mention of the possible need for starting at a lower dose, or what populations might need caution when initiating therapy as described in the approved labeling. He did not discuss the possible need for dosage titration in certain populations.

These promotional labeling pieces and the teleconference are considered to be false and misleading and in violation of the Act. DDMAC requests the following actions:

1. Immediately discontinue the use of all promotional labeling pieces, and cancel all advertisements containing any of the false and/or misleading statements discussed above.

2. Provide DDMAC with a complete listing of all advertisements and labeling pieces that will be canceled, and those that will continue in use. Also provide copies of these various pieces to DDMAC.

3. Provide DDMAC with a listing of all state formulary committees, health care groups' formulary or therapeutics committees, hospital therapeutics or formulary committees, or any other body engaged in the selection for inclusion or exclusion of drug products from their respective formularies or drug lists, that Lilly provided information similar to that discussed above.

4. Provide a written statement that Lilly will agree to number 1 - 3 above, no later than November XX, 1996.

If Lilly has any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Lilly that only written communications are considered official.

In all future correspondence regarding this specific issue, please refer to the MACMIS ID # 4782, in addition to the NDA number.

Sincerely,

Kenneth R. Feather

Kenneth R. Feather
Senior Advisor
Division of Drug Marketing,
Advertising and Communications

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