



NDA 20-592 / S-018

Eli Lilly and Co., Inc.
Attention: Gregory T. Brophy, Ph.D.
Lilly Corporate Center
Indianapolis, Indiana 46285
USA

Dear Dr. Brophy:

Please refer to your supplemental new drug application (NDA) dated September 16, 2002, received September 17, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyprexa (olanzapine) Tablets, 2.5, 5, 7.5, 10, 15, and 20 mg. This supplemental NDA provides for the use of olanzapine in combination with lithium or valproate for the treatment of acute manic episodes associated with bipolar disorder.

We also acknowledge receipt of your amendments dated September 26, 2002 and November 13, 2002 (FAX).

Approval of Supplemental Application with Agreed-Upon Labeling Text (Enclosed)

We have completed the review of this application as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed agreed-upon labeling text (package insert). Accordingly, this application is approved, effective on the date of this letter.

Submission of Final Printed Labeling (FPL)

The final printed labeling (FPL) must be identical to the enclosed agreed-upon labeling text for the package insert. Please submit the FPL electronically according to the Guidance for Industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please mount individually ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL For Approved Supplement NDA 20-592/S-018" regardless of the medium chosen for its submission (paper or electronic). FDA approval of this additional submission of FPL is not required before the labeling is used.

CMC: Categorical Exclusion

We have completed our review of the information provided by your firm, and we agree with your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application.

Pediatric Rule: Pediatric Waiver Request

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] has been challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule

and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, intervening third parties have decided to appeal the court's decision striking down the rule.

We note Lilly's ongoing commitment to the conduct of a pediatric study of olanzapine as monotherapy in adolescent patients diagnosed with manic or mixed episodes associated with bipolar I disorder (with or without psychotic features). We also note that on May 30, 2002, which predates the court ruling on the Pediatric Rule, the Division granted Lilly a waiver from the then-existing requirement to conduct pediatric studies of olanzapine in combination with lithium or valproate. The Division has determined that this waiver would be upheld if the Pediatric Rule is upheld or a similar rule enacted.

However, the pediatric exclusivity provisions of FDAMA, as reauthorized by the Best Pharmaceuticals for Children Act, are not affected by the court ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on the FDA Web site at www.fda.gov/cder/pediatric) for details.

If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request to as being responsive to the Written Request. Applicants should therefore obtain a Written Request before submitting such pediatric studies to an NDA.

Promotional Materials

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

"Dear Health Care Professional" Letters

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at 301-594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure (Agreed-Upon Labeling)
[The electronic signature page will follow the labeling.]

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz

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