

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
February 6, 2008**

Topic: The committee discussed new drug application (NDA) 22-173 ZYPREXA ADHERA (olanzapine pamoate depot) long acting intramuscular (IM) injection 210 mg, 300 mg, and 405 mg per/vial, Eli Lilly and Company, for treatment of schizophrenia. A particular safety concern for discussion was the occurrence of severe somnolence in some patients who are administered this depot formulation of olanzapine.

These summary minutes for the February 6, 2008 Psychopharmacologic Drugs Advisory Committee meeting were approved on February 13, 2008.

I certify that I attended the February 6, 2008 Psychopharmacologic Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

-S-
Diem-Kieu H. Ngo, Pharm.D.
(Designated Federal Official)

-S-
Matthew V. Rudorfer, M.D.
(Acting Chair)

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting February 6, 2008

The following is the final report of the Psychopharmacologic Drugs Advisory Committee meeting held on February 6, 2008. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at

<http://www.fda.gov/ohrms/dockets/ac/cder08.html#Psychopharmacologic>

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration met on February 6, 2008 at the Crowne Plaza Silver Spring, 8777 Georgia Avenue, Silver Spring, Maryland. Matthew V. Rudorfer, M.D., chaired the meeting. There were approximately 150 in attendance.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members present (voting):

Rochelle Caplan, M.D.; Gail W. Griffith, M.L.S. (Consumer Representative); Barbara G. Wells, Pharm.D.

Psychopharmacologic Drugs Advisory Committee Members absent:

Daniel S. Pine, M.D. (Chair); Jorge Armenteros, M.D.; Robert W. Buchanan, M.D.; Bruce G. Pollock, M.D., Ph.D.; Delbert G. Robinson, M.D.; Susan K. Schultz, M.D.; Marcia J. Slattery, M.D., M.H.S.; Robert F. Woolson, Ph.D.

Temporary Voting Members:

Barbara Geller, M.D.; Andrew Leon, Ph.D.; J. John Mann, M.D.; Matthew V. Rudorfer, M.D. (Acting Chair); David Shaffer, F.R.C.P., F.R.C.Psych.; Andrew Winokur, M.D., Ph.D.; Dean A. Follmann, Ph.D.; Margy Lawrence (Patient Representative).

Industry Representative (non-voting):

William Z. Potter, M.D., Ph.D. (PDAC)

FDA Participants (non-voting):

Robert Temple, M.D.; Thomas Laughren, M.D.; CDR Mitchell Mathis, M.D.; Gwen Zornberg, M.D.

Open Public Hearing Speaker:

Vince Boehm

On February 6, 2008, the committee met to discuss new drug application (NDA) 22-173 ZYPREXA ADHERA (olanzapine pamoate depot) long acting intramuscular (IM) injection 210 mg, 300 mg, and 405 mg per/vial, Eli Lilly and Company, for treatment of schizophrenia. A particular safety concern for discussion was the occurrence of severe somnolence in some patients who are administered this depot formulation of olanzapine.

On February 6, 2008, Matthew V. Rudorfer, M.D., (Acting Chair) called the meeting to order at 8:00 a.m. The Committee members and the FDA participants introduced themselves. The conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., Designated Federal Official (DFO).

The agenda for the meeting was as follows:

8:00 a.m. Call to Order and Opening Remarks

Matthew Rudorfer, M.D.
Acting Chair,
Psychopharmacologic Drugs Advisory Committee

Introduction of Committee

Conflict of Interest Statement

Diem-Kieu H. Ngo, Pharm.D., BCPS
Designated Federal Official

8:15 a.m. FDA Introductory Remarks

Thomas Laughren, M.D.
Director, Division of Psychiatry Products,
Office of Drug Evaluation I, OND, CDER, FDA

FDA PRESENTATION

8:20 a.m. FDA Clinical Review of Olanzapine
Pamoate Depot in the Treatment of
Schizophrenia

Jing Zhang, M.D., Ph.D.
Medical Officer, Division of Psychiatry Products,
Office of Drug Evaluation I, OND, CDER, FDA

8:50 a.m. Exposure-Safety Assessment

Andre Jackson, Ph.D.
Division of Clinical Pharmacology 1,
Office of Clinical Pharmacology, OTS, CDER, FDA

9:00 a.m. Clarifying Questions

9:30 a.m. **BREAK**

INDUSTRY PRESENTATION

9:45 a.m. Introduction and Overview

Gregory Brophy, Ph.D.
Director, U.S. Regulatory Affairs
Eli Lilly and Company

9:50 a.m. Schizophrenia and Adherence
to Medication

John Kane, M.D.
Chairman, Department of Psychiatry
Zucker Hillside Hospital, NY

10:00 a.m. Product and Development,
Pharmacokinetics, OP Depot
Efficacy in Schizophrenia

David McDonnell, M.D.
Clinical Research Physician
Eli Lilly and Company

10:25 a.m. OP Depot Safety in Schizophrenia

Sara Corya, M.D.
Medical Director
Eli Lilly and Company

11:05 a.m. Benefit-Risk Assessment & Conclusion

John Lauriello, M.D.
Professor and Vice Chair, Department of Psychiatry
University of New Mexico
Executive Medical Director of UNM Psychiatric Center

11:15 a.m. Clarifying Questions

11:30 a.m. OP Depot Reconstitution

Eli Lilly and Company
Demonstration Video

12:00 p.m. **LUNCH**

1:00 p.m. Open Public Hearing

2:00 p.m. Questions/Clarifications

3:00 p.m. **BREAK**

3:15 p.m. Panel Discussion/Questions

5:00 p.m. **ADJOURNMENT**

Questions to the Committee:

1. What are the public health consequences of a depot antipsychotic that leads unpredictably to profound sedation in 1% or more of patients exposed to this product (Discuss and Comment)?

Committee Discussion:

The committee noted that there would be significant public health consequences (both positive and negative) of OP Depot. There seemed to be a predominant view among committee members that it would be worth trying to manage the risks of this new product in order to make it available to clinicians. The consensus view seemed to be that a mandatory observation period was needed; however, there was not clear agreement on exactly how long that period would need to be. (Most discussion focused on either three hours of monitoring post-injection at the treatment site, or one hour of monitoring at the site followed by two hours of accompaniment by a responsible companion). There was concern, however, of a possibly greater risk of this excessive sedation event when this product would be used in a “real world” setting outside of clinical trials. The Committee also noted that the description of the toxicity under discussion as “profound sedation” might minimize its clinical significance, and suggested incorporation of the typical accompanying delirious state into the description. (See Transcript for Complete Discussion)

2. If OP Depot were to be approved and marketed, what risk management procedures would be necessary, including labeling advice, to ensure the safe use of this product? For example, would the labeling changes include a second line status and a black box warning (Discuss and Comment)?

Committee Discussion:

The committee noted concerns over “casual use” of OP Depot if labeling is not clear. The committee commented that the safety issues for OP Depot are above and beyond those of other available depot antipsychotics; thus, some restrictions on the use of OP Depot may be appropriate. The committee recommended that the label include the following: a mandatory observation period post injection (no clear agreement on how long this should be: possibly some combination of monitoring at the site and accompaniment by a responsible companion totaling at least three hours), and language limiting use to patients with documented non-adherence to oral antipsychotics. The committee further suggested that patients should be involved in the decision making process (discussion between patient and provider regarding the risks versus benefits). The committee seemed opposed to relegating OP Depot to a second line status, preferring instead to allow clinicians to make the judgment calls regarding when to use it. A

suggestion was made that labeling include the notation that women and ethnic minority individuals were underrepresented in the clinical trials in which the profound sedation/delirium adverse effects were observed. (See Transcript for Complete Discussion)

3. Has OP Depot been shown to be effective for the treatment of acutely exacerbated schizophrenic patients (Yes/No)?

Committee Discussion:

(See Transcript for Complete Discussion)

Yes: 11 No: 0 Abstain: 0

4. Has OP Depot been shown to be effective for the maintenance treatment of schizophrenic patients (Yes/No)?

Committee Discussion:

(See Transcript for Complete Discussion)

Yes: 11 No: 0 Abstain: 0

5. Has OP Depot been shown to be acceptably safe for the treatment of acutely exacerbated schizophrenic patients (Yes/No)?

Committee Discussion:

(See Transcript for Complete Discussion)

The committee proposed to change the wording of the question to:

Are there circumstances under which OP Depot would be acceptably safe for the treatment of acutely exacerbated schizophrenic patients (Yes/No)?

Yes: 10 No: 0 Abstain: 1

6. Has OP Depot been shown to be acceptably safe for the maintenance treatment of schizophrenic patients (Yes/No)?

Committee Discussion:

(See Transcript for Complete Discussion)

The committee proposed to change the wording of the question to:

Are there circumstances under which OP Depot would be acceptably safe for the maintenance treatment of schizophrenic patients (Yes/No)?

Yes: 10 No: 0 Abstain: 1

The meeting was adjourned at approximately 4:30 p.m. on February 6, 2008.