Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

October 25-26, 2005

Members Present (Voting)
Wayne Goodman M.D. (Chair)
Jean Bronstein, R.N., M.S.
Andrew Leon, Ph.D.
James McGough, M.D.
Delbert Robinson, M.D.
Daniel Pine, M.D.
Bruce Pollock, M.D., Ph.D.
Philip Wang, M.D., M.P.H., Dr. P.H.

Consultants to the Psychopharmacologic Drugs Advisory Committee (Voting)
Gail Griffith, B.A., M.A. (Patient Representative)
Matthew Rudorfer, M.D.
Carol Tamminga, M.D.
Andrew Winokur, M.D.

Psychopharmacologic Drugs Advisory Committee Industry Representative (Non-voting)
Dilip Mehta, M.D., Ph.D.

FDA Participants
Thomas Laughren, M.D.
Paul Andreason, M.D.
Gregory Dubitsky, M.D.

Acting Executive Secretary
Karen M. Templeton-Somers, Ph.D.

Member Not Present
Barbara Wells, M.D., Ph.D.

These summary minutes for the October 25-26, 2005 meeting of the Psychopharmacologic Drugs Advisory Committee were approved on November 21, 2005.

I certify that I attended the October 25-26, 2005 meeting of the Psychopharmacologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Karen M. Templeton-Somers, Ph.D.
Acting Executive Secretary

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Wayne K. Goodman, M.D.
Chair

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and written statements submitted by the public. On October 25, 2005, the meeting was called to order by Wayne Goodman, M.D. (Committee Chair); the conflict of interest statement was read into the record by Karen M. Templeton-Somers, Ph.D. (Acting Executive Secretary). There were approximately 180 in attendance.

Attendance on October 25, 2005:
Psychopharmacologic Drugs Advisory Committee Members Present (voting):
Wayne Goodman, M.D.(Chair), Jean Bronstein, R.N., M.S., Andrew C. Leon, Ph.D., James McGough, M.D., Delbert Robinson, M.D., Bruce Pollock, M.D., Ph.D., Daniel Pine, M.D., Bruce G. Pollock, M.D. Ph.D , Philip Wang, M.D., M.P.H., Dr. P.H.

Psychopharmacologic Drugs Advisory Committee Member (Industry Representative- non-voting):
Dilip Mehta, M.D., Ph.D.

Psychopharmacologic Drugs Advisory Committee Consultants (voting):
Matthew Rudorfer, M.D., Carol Tamminga, M.D., Andrew Winokur, M.D.

Psychopharmacologic Drugs Advisory Committee Patient Representative (voting):
Gail Griffith

FDA Participants at the Table:
Thomas Laughren, M.D., Paul Andreason, M.D.

Open Public Hearing Speakers (October 25, 2005):
Darrel Regier - American Psychiatric Association
A.G. Awad - International Society for CNS Clinical Trials and Methodology
Suzanne Vogel-Scibilia - National Alliance on Mental Illness

Topic: issues and questions pertinent to the need for longer term efficacy data for proposed drug treatments for chronic psychiatric disorders, and issues and questions pertinent to optimal study designs for obtaining valid information about longer-term benefits of drug treatment

Overview of Issues and Questions	Thomas Laughren, M.D. Director, Division of Psychiatry Products CDER, FDA
Presentations from Industry	
Introductory Remarks and Review of Agenda	Mark Ammann, Pharm.D. Pfizer Global Research and Development
Introduction/Overview	Frederick Goodwin, M.D. George Washington University
Rationale for Long-Term Treatment	Earl Giller, M.D. Pfizer Global Research and Development
Disease and Compound Specific Approaches to the Development of Psychotherapeutic Agents	Robert A. Leadbetter, M.D. GlaxoSmithKline
Informative Studies of New Therapeutic Agents in Major Depression, GAD & Panic	W. Z. Potter, M.D., Ph.D. Merck Research Laboratories
Key Questions Engendered by Proposal to Change Long-Term Efficacy Requirements	Joseph Camardo, M.D. Wyeth Pharmaceuticals

Issues with Long-Term Trials in Bipolar Disorder	Gary Sachs, M.D. Harvard Medical School Massachusetts General Hospital
Long-Term Anti-Psychotic Trials: Challenges and Opportunities	Mihael Polymeropoulos, M.D. Vanda Pharmaceuticals
Long-Term Anti-Psychotic Treatment in Schizophrenia: 30 Years of Data and Experience	Nina Schooler, Ph.D. Department of Psychiatry Georgetown University School of Medicine
Some Statistical Issues Regarding the Use of Active Versus Placebo Controls in Longer-Term Efficacy Trials	Gene Laska, Ph.D. Nathan Kline Institute for Psychiatric Research NYU School of Medicine
Timing and Duration of Relapse Prevention Trials in Psychiatric New Drug Development	David Michelson, M.D. Eli Lilly and Company
Concluding Remarks	Frederick Goodwin, M.D. George Washington University

Open Public Hearing

Questions from the Committee to Sponsor and FDA

Committee Discussion

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Questions to the Committee

We have developed a list of questions that we would like the committee to address during the discussion phase of the meeting. For purposes of simplifying the discussion, we will focus the initial questions (Questions 1 through 8) on Major Depressive Disorder (MDD), and then return later to expand the questions to any chronic psychiatric disorder. [Note: We are asking for a vote on questions 1 and 2, while for others, discussion and comments would suffice.]

1. **Is it a reasonable expectation that a sponsor would have accumulated data for both acute and longer-term efficacy trials at the time of filing of an application for a drug for the treatment of MDD?**

Yes – 0 *No – 12* *Abstain – 0*

The Committee interpreted this question as saying that the longer-term efficacy data would be completed, analyzed and included in the new drug application. The Committee consensus was that this is too strict a requirement to incorporate into the new drug application, and could result in slowing the process of new drug development. However, the Committee was also clear in stating the need for better data on longer-term efficacy and safety, and would like to see sponsors making a stronger commitment to completing high quality, well-designed Phase IV studies in a timely manner. There was also concern that the information learned from these trials should be made available to the public.

Questions 2 through 11 were not addressed by the Committee, but are included at the end of this document.
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Statement from the Committee: The Committee drafted the following statement, and voted to express their support:

"The Advisory Committee recognizes the need for evidence to inform clinical practice regarding long-term treatment efficacy, without potentially slowing progress of new drug development. We encourage collaborative efforts by industry, NIH, and the FDA to further research in long-term treatment."

Yes – 12 *No – 0* *Abstain – 0*

The Committee emphasizes the need for more effective treatments, and for more data on the already available treatments, especially regarding longer-term efficacy and safety.

The Committee also indicated that no other psychiatric disorder would require long-term efficacy studies before approval for an acute indication, and recommended that specialized groups be convened to consider the research needs for specific disorders.

12. If there are data supporting a longer-term claim for adults for a drug for a chronic psychiatric indication, is there a need to obtain longer-term data for a pediatric indication for this same disorder, or would it be sufficient to obtain acute data for the pediatric population and extrapolate from adult data for the longer-term claim? [Discussion requested]

The Committee emphasized that pediatric disorders differ greatly from the adult, and that the treatments will differ in the two populations. Efficacy and safety data do not extrapolate well from the adult population to the pediatric one, and possibly not to the geriatric population. Differences in pharmacokinetics and developmental neurology make long-term safety data necessary for pediatric indications.

It was also indicated that the needs for pediatric studies are disorder-specific, and would be better addressed by specialized groups. However, in general, there is a need for more longer-term studies, of both safety and efficacy, in children.

The Meeting adjourned for the day at approximately 4:00 p.m. and reconvened on October 26, 2005 at 8:00 a.m.

Questions 2 through 11 were not specifically addressed by the Committee.

2. If the answer to question 1 is yes, is it a reasonable expectation that the sponsor must have demonstrated both acute and longer-term efficacy for MDD? **[Vote requested]**

For those voting No on this question, 2 additional questions [Note: When asking for longer-term trials as a phase 4 commitment at the time of approval of an acute claim, it has been our standard to request a single longer-term trial. In the one situation where a sponsor submitted an application based only on longer-term data, we required 2 positive longer-term trials to support the claim.]:

a. If the acute studies support an acute claim, but the longer-term trial fails to demonstrate an effect, could the drug be approved for short-term use, with a mention of the negative longer-term findings in the label? **[Vote requested]**

b. If the longer-term studies support a maintenance claim, but the acute trials fail to demonstrate an effect, could the drug be approved for maintenance treatment, with a mention of the negative acute findings in the label? [Note: We have, in fact, already approved a drug for maintenance treatment in the absence of acute efficacy, i.e., Lamictal for bipolar maintenance, however, without mention of the negative acute findings in the label.] **[Vote requested]**

3. If the answer to question 1 is yes, at what point in a development program for a drug for MDD should this new requirement for longer-term data at the time of filing of an application be implemented? **[Discussion requested]**

4. What is the minimum period of time that patients with MDD should remain in a responder status before being randomized in a randomized withdrawal study? An extension to this question is whether or not this duration should be different depending on whether this is a monotherapy or an add-on maintenance trial? **[Discussion requested]**

5. Would it be reasonable to accept minor and temporary excursions above criterion scores for "responder" status for MDD patients in an open run-in phase, or minor dosage adjustments, and still consider such patients to have remained in a "responder" status? **[Discussion requested]**

6. Would it be reasonable to accept minor and temporary excursions above criterion scores for MDD patients in the randomized phase, and even slight dose adjustments, without considering such patients to have relapsed? **[Discussion requested]**

7. Should placebo responders during a double-blind phase of an acute trial, who are switched to active drug during a continuation phase, be considered for randomization in a randomized withdrawal trial, i.e., should they be considered similar to (or different from) patients who responded on active drug and were then continued on active drug for longer-term stabilization? **[Discussion requested]**

8. Should sponsors be encouraged (or even required) to utilize fixed dose randomized withdrawal studies rather than randomizing MDD patients to their optimal dose during the run-in phase? **[Discussion requested]**

9. Would the answers to any of the questions change in considering other chronic psychiatric disorders? **[Discussion requested: Note—It isn't necessary or possible to discuss every chronic psychiatric disorder at this one-day meeting. Rather, we are trying to get a sense of whether or not, if you agree with a requirement for longer-term data, that requirement should be applied generally to all chronic psychiatric disorders. If not, what are the exceptions to the rule? In addition, should the course of long-term illness (e.g., chronic with discrete episodes, cyclical, or persistent symptoms) determine the specific design of the longer-term trial needed to show longer-term efficacy?]**

10. Are there alternative designs that should be considered for establishing longer-term efficacy [Note: We are happy to consider discussion of the suggestion of active-controlled comparisons in longer-term trials for schizophrenia, however, until more data are accumulated and presented, we are not likely to consider this issue ripe for resolution.]? **[Discussion requested]**

11. Information about longer-term efficacy from such a trial is generally located in 3 different sections of labeling: (1) Clinical Trials, under Clinical Pharmacology; (2) Indications and Use; and (3) Dosage and Administration. To illustrate what is the division's current approach to including this kind of information in labeling, we have included here language from these sections of labeling for the drug Zyprexa:

Clinical Pharmacology/Clinical Trials

Bipolar Disorder

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar disorder who had responded during an initial open-label treatment phase for about two weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to $\leq$ 12 and HAM-D 21 to $\leq$ 8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-

D 21 total score to ≥ 15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Indications and Usage

Bipolar Disorder
Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA after achieving a responder status for an average duration of two weeks was demonstrated in a controlled trial (see Clinical Efficacy Data under CLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Dosage and Administration

Bipolar Disorder
Maintenance Monotherapy — The benefit of maintaining bipolar patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of two weeks, was demonstrated in a controlled trial (see Clinical Efficacy Data underCLINICAL PHARMACOLOGY). The physician who elects to use ZYPREXA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Is this language a reasonable interpretation and translation of the data from the longer-term trial that supported the longer-term claim for Zyprexa in bipolar disorder, or is there a better way of presenting this information in labeling? **[Discussion requested]**

October 26, 2005

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Psychopharmacologic Drugs Advisory Committee Member (Industry Representative- non-voting):
Dilip Mehta, M.D., Ph.D.

Psychopharmacologic Drugs Advisory Committee Consultants (voting):
Matthew Rudorfer, M.D., Carol Tamminga, M.D., Andrew Winokur, M.D.

Psychopharmacologic Drugs Advisory Committee Patient Representative (voting):
Gail Griffith

FDA Participants at the Table:
Thomas Laughren, M.D., Paul Andreason, M.D. , Gregory Dubitsky, M.D.

Open Public Hearing Speakers: There were no speakers at the Open Public Hearing.

Topic: discuss the question of whether or not dietary restrictions would be needed for the 20 mg dose for Emsam (selegiline transdermal system) [new drug applications (NDA) 21-336, short-term claim, and NDA 21-708, longer-term claim, Somerset Pharmaceuticals], for the treatment of major depressive disorder.

FDA Presentation	Gregory Dubitsky, M.D. Medical Officer Division of Psychiatry Products, CDER
Sponsor Presentation	Somerset Pharmaceuticals
Introduction	Melissa L. Goodhead, B.Sc., RAC- Moderator Group Director, Regulatory Affairs/Quality Assurance Somerset Pharmaceuticals, Inc.
Overview	Sheldon Preskorn, M.D. Chairman, Department of Psychiatry University of Kansas, Wichita
Safety- Tyramine	Lawrence Blob, M.D. Medical Director, Somerset Pharmaceuticals, Inc.
Education & Communication of Dosing Instructions	Chad VanDenBerg, Pharm.D. Director of Clinical Programs & Product Information
Conclusions	Lawrence Blob, M.D.
Questions and Answers	Melvin Sharoky, M.D. CEO and President, Somerset Pharmaceuticals, Inc.

Questions to the Committee (there were 11 voting Members in attendance for Question 1, and 10 for Question 2)

1. **Do the available data for the Emsam 20 mg patch support the reasonable safety of this formulation without the need for dietary restrictions? [Vote requested]**

   Yes – 7 *No – 4* *Abstain – 0*

   The Committee indicated that more choices are needed for treatment of Major Depressive Disorder, and that this product represents a new approach to a currently under-used molecular entity, with risks lower than for tranylcypromine. A dosage form without dietary restrictions would be valuable in treating this highly heterogeneous disorder, especially for the highly refractory patients.

   The Committee felt that the pivotal studies have not clarified the dose-response relationship sufficiently, and that the population studied was too small to provide reliable safety data. There is also concern about the patient interpretation of the dietary restrictions, and that the information as currently presented could be misunderstood, leading to error in use.

2. **If the Emsam 20 mg patch formulation could be considered reasonably safe for marketing without the need for dietary restrictions, would it be acceptable to market the 20 mg patch without dietary restrictions and at the same time require dietary restrictions for the 30 and 40 mg patch strengths? [Vote requested]**

   Yes – 6 *No – 4* *Abstain – 0*

   Some of the Committee's concerns about the marketing of the 20 mg patch without dietary restrictions at the same time the 30 and 40 mg patches are marketed with the dietary restrictions include:

- *A reluctance to titrate to the higher dose, perhaps inappropriately, because of a desire to avoid the dietary restrictions*
- *Confusion about which doses require the dietary restrictions, especially with the proposed labeling (which include the amount of drug that is bioavailable, as well as the dosage). It was also suggested that the dosage be marked on the individual patches, as well as on the box. Instructions on using only one patch per day must be clear.*
- *The current list of restricted foods must be made more clear and understandable.*
- *A need for a better education plan, for both clinicians and patients*

The Committee suggested that further studies on the pharmacology of the product might support removal of the dietary restrictions from the higher dosage levels.

The meeting adjourned at approximately 1:00 p.m.