Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE CDER PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

August 4, 2005

Members Present (Voting)
Karl Kieburtz, M.D., M.P.H (Acting Chair)
Michael Hughes, Ph.D.
Carol Koski, M.D.
Ralph Sacco, M.D., M.S.

FDA Participants
Robert Temple, M.D.
Russell Katz, M.D.
Eric Bastings, M.D.
Mary Ross Southworth, M.D.

Executive Secretary
Anuja M. Patel, M.P.H.

Consultants to the Peripheral and Central Nervous System Drugs Advisory Committee (Voting)
Lily Jung, M.D., M.M.M. (Consumer Representative)
Larry Goldstein, M.D.
Stanley Fahn, M.D.
Marc Lenaerts, M.D.
Kenneth Welch, M.B., Ch.B., F.R.C.P
Sheila Weiss Smith, Ph.D., F.I.S.P.E.
Mark Green, M.D.

Federal Government Employee Consultant (Voting)
Dilip Jeste, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee Industry Representative (Non-voting)
Roger Porter, M.D.

These summary minutes for the August 4, 2005, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee were approved on ___August 18, 2005___

I certify that I attended the August 4, 2005, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

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Anuja Patel, M.P.H.
Executive Secretary

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Karl Kieburtz, M.D.
Acting Chair

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the sponsors. The meeting was called to order by Karl Kieburtz, (Acting Committee Chair); the conflict of interest statement was read into the record by Mary Ann Killian (Program Integrity Advisor, Ethics and Integrity Staff). There were approximately 120 persons in attendance. There was one speaker for the Open Public Hearing session.

Open Public Hearing Speaker:
Cynthia McCormick, M.D.

Issue:

Discussions on new drug application (NDA) 21-645, proposed trade name MT100 (naproxen sodium and metoclopramide hydrochloride) Tablets, Pozen, Inc., for the proposed indication of acute treatment of migraine headache with or without aura.

FDA Presentation

• Opening Remarks Overview of Issues	Russell Katz, M.D. Director, Division of Neurology Products, FDA

Sponsor Presentation

POZEN Incorporated

• Introduction and Summary	Marshall E. Reese, Ph.D. Executive Vice President, Product Development Pozen Incorporated
• Overview of Tardive Dyskinesia	A.H.V. (Tony) Schapira, M.D. Professor of Neurology, Royal Free Hospital School of Medicine London, United Kingdom
• Review of MT100 Efficacy	William James Alexander, M.D., M.P.H., F.A.C.P Senior Vice President, Clinical Development Chief Medical Officer Pozen Incorporated
• Potential Role of MT100 in Migraine Therapy: Balancing Benefits and Risks	David B. Matchar, M.D., F.A.C.P. Director, Duke Center for Clinical Health Policy Research Professor of Medicine Duke University School of Medicine
• Clinical Considerations on Migraine Treatment	Stephen D. Silberstein, M.D. Director, Jefferson Headache Center Thomas Jefferson University Hospital

FDA Presentation

• FDA Risk/Benefit Considerations	Eric Bastings, M.D. Clinical Team Leader, DNP, FDA
• Overview of Tardive Dyskinesia	Hyder A. Jinnah, M.D., Ph.D. The Johns Hopkins Hospital
• Post-marketing Review of Movement Disorders and Neuroleptic Malignant Syndrome Associated with Metoclopramide	Mary Ross Southworth, Pharm.D. Safety Evaluator, Division of Drug Risk Evaluation, Office of Drug Safety, FDA

Questions for Advisory Committee

1. Pozen estimated an annual incidence of tardive dyskinesia (TD) of up to 0.038% for metoclopramide at a daily dose of 30-40 mg/day for 72 days/year (which corresponds to up to 380 cases of TD per million patients per year).

- Do you think that this is a reasonable estimate?

  Yes = 1 No = 11 Abstain = 0 Total = 12

  Seven of the 11 members who voted "No" said that they did not know what the recommended estimate should be. Three of the 11 members who voted "No" said that they think the estimate should be higher. The Chair voted "Yes" and suggested that a reasonable estimate could be between 0 and 1. The Committee also suggested ways of obtaining a better estimate.

  Please see transcript for details.

- If MT100 were to carry the same risk, would such a risk level be acceptable if the only contribution of metoclopramide is a 5-10% improvement on sustained headache relief (with no effect on 2-h endpoints)?

  Yes = 2 No = 10 Abstain = 0 Total = 12

  The Chair summarized that the majority of the Committee felt that the 2-h endpoints were critical and most significant. The amount of benefit demonstrated thus far, without stating its significance or not, was not sufficient given the perceived risk and the absence of benefit at 2 hr endpoints.

  Please see transcript for details.

- Is any risk of tardive dyskinesia acceptable for a migraine population?

  Yes = 12 No = 0 Abstain = 0 Total = 12

  Please see transcript for details.

2. Is there sufficient evidence that the chronic-intermittent administration of metoclopramide does not carry a risk of tardive dyskinesia?

   Yes = 0 No = 12 Abstain = 0 Total = 12

- Is it possible to define a maximum recommended number of monthly doses of MT100 to avoid the risk of tardive dyskinesia?

  Yes = 0 No = 12 Abstain = 0 Total = 12

  The Chair summarized that the Committee felt that there was not enough evidence that there was no risk of tardive dyskinesia with chronic intermittent administration; nor could the Committee identify a dose that would be below the risk or no risk.

  Please see transcript for details.

3. Do you believe that, based on the existing data on medication-overuse headache, there is evidence that a proportion of patients prescribed MT100 will likely take a number of monthly doses higher than recommended?

Yes = 12 *No = 0* *Abstain = 0* *Total = 12*

The Committee felt that it was likely that no matter how the drug was labeled and approved that individuals would take the medication more than the recommended dosage if there was a limitation on the number of dosages.

Please see transcript for details.

4. All currently approved acute treatments of migraine are indicated without restriction regarding the presence or absence of nausea at baseline.

- Given that patients may have nausea at some attacks and no nausea at others, does an indication limited to the subpopulation of migraine patients with no nausea at baseline represent a clinically meaningful and acceptable indication?

Yes = 0 *No = 9* *Abstain = 3* *Total = 12*

The Committee was not in support of individuals without nausea at baseline being an identifiable group of a clinically meaningful acceptable indication. The Committee felt that there was an uncertainty whether the nausea or no nausea populations that have been demonstrated and that the Sponsor should not mislead itself by a sub group analysis post hoc that may lead them down the wrong path.

Please see transcript for details.

5. If Pozen shows prospectively in a new clinical study in migraine patients with no nausea at baseline:
   - a significant contribution of metoclopramide on sustained headache pain relief of 5-10%
   - no contribution of metoclopramide at 2-hours
   - no contribution of metoclopramide on relapse rate or rescue medication use in the 2-24 hour period,

   - Would the demonstrated benefit outweigh the risks related to tardive dyskinesia?

Yes = 0 *No = 12* *Abstain = 0* *Total = 12*

   - If not, what additional data (or desired primary outcome, or desired effect on sustained relief) could provide evidence of safety and efficacy?

The Committee felt that additional safety data was needed, and that the 2 h endpoint was important. In addition, the Committee was concerned with the ways subjects may access the medication through specific failure of other intervention prior to the exposure of this intervention.

Please see transcript for details.

Following completion of discussion of the questions, the committee adjourned at approximately 3:30 PM.