Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee
December 6, 2007

The following is the final report of the meeting of the Peripheral and Central Nervous System Drugs Advisory Committee held on December 6, 2007. 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/cder07.htm#

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

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration met on December 6, 2007 at the Sheraton College Park Hotel, located at 4095 Powder Mill Road, Beltsville, Maryland. Larry B. Goldstein, M.D. chaired the meeting. There were approximately 210 in attendance.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Member:

Britt Anderson, M.D., Ph.D., James R., Couch Jr., M.D., Ph.D. F.A.C.P., Mark W. Green, M.D., Larry B. Goldstein, M.D., Gregory L. Holmes, M.D., Lily K.F. Jung, M.D., M.M.M.*(Consumer Representative)*, Matthew Rizzo, M.D. *(Participated by telephone)*, Stacy Ann Rudnicki, M.D., Ying Lu, Ph.D.

Peripheral and Central Nervous System Drugs Advisory Committee absent Members:
Karl D. Kieburtz, M.D., M.P.H. (Chair), Sandra F. Olson, M.D.

Temporary Voting Members:
Howard Hurtig, M.D., Carolyn L. Koski, M.D., Karen S. Milek *(Patient Representative)*

Industry Representative: (non-voting):
Roy E. Twyman, M.D.

FDA Participants:
Robert Temple, M.D., Russell Katz, M.D., Alice Hughes

Open Public Hearing Speakers:
Nancy S. Wexler, Ph.D., Lavonne V. Goodman, M.D., Barbara Boyle, Maria Hardin, Katharine Moser, Anne Pae, Gabrielle Hamilton, L.C.S.W., Gary and Barbara Parker, Wesley Johnston, Cindy Diogo, Ann M. Russo, Daniel Born, Ph.D., Jonathan Monkemeyer, Deborah Fine.

On December 6, 2007 the committee met to discuss new drug application (NDA) 21-894, *tetrabenazine*, submitted by Prestwick Pharmaceuticals Inc. for the proposed indication to treat chorea associated with Huntington's disease.

Larry B. Goldstein, M.D. (Acting Chair), called the meeting to order at 8:00 a.m. The Panel members and the FDA participants introduced themselves. The conflict of interest statement was read into the record by Darrell Lyons, BSN, Designated Federal Officer (DFO), the agenda preceded as follows:

8:00	Call to Order Introduction of Committee	**Larry B. Goldstein, M.D.** Acting Chair, PCNS
	Conflict of Interest Statement	**Darrell Lyons, B.S.N., R.N.** Designated Federal Official

8:15	Welcome and Introductory Comments	**Russell Katz, M.D., Director** Division of Neurology Products, CDER, FDA
8:30	**SPONSOR PRESENTATIONS**	
	Introduction	**Martin Stogniew, Ph.D.** Executive Vice President Prestwick Pharmaceuticals, Inc.
	Overview of Huntington's disease	**Joseph Jankovic, M.D.** Professor of Neurology Baylor College of Medicine
	Clinical Efficacy	**Fred Marshall, M.D.** Associate Professor of Neurology, Chief, Geriatric Neurology Unit and the Huntington Study Group University of Rochester
	Non-Motor Endpoints	**Peter Como, Ph.D.** Associate Professor of Neurology, Clinical Psychiatry, and Brain and Cognitive Sciences, and the Huntington Study Group, University of Rochester
	Clinical Safety	**David Stamler, M.D.** Chief Scientific Officer Prestwick Pharmaceuticals, Inc.
	Safety and Efficacy of Tetrabenazine	**Ira Shoulson, M.D.** Professor of Neurology, Medicine, Pharmacology & Physiology Louis C Lasagna Professor of Experimental Therapeutics and Chair, Huntington Study Group, University of Rochester
10:00	Questions to Sponsor	
10:15	***Break***	
10:30	**FDA PRESENTATIONS**	
	Efficacy Considerations	**Carole Davis, D.O., Medical Officer** Division of Neurology Products, CDER, FDA
	Dose-Response Analysis for Effectiveness and Safety	**Atul Bhattaram, Ph.D., Pharmacometrics Reviewer** Pharmacometrics, Office of Clinical Pharmacology, FDA
	Safety Review	**Lourdes Villalba, M.D., Medical Officer** Division of Neurology Products, CDER, FDA
12:00	*Questions to FDA*	
12:15	***Lunch***	
1:15	***Open Public Hearing***	

2:15 ***Break***

2:30 *Committee Questions and Panel Discussion*

5:00 ***Adjourn***

Questions to the Committee:

1. Do the findings on the secondary efficacy outcomes (lack of a beneficial effect of tetrabenazine on numerous measures of function and cognition and/or numerical superiority of placebo on some measures) by themselves raise sufficient concerns about the utility of tetrabenazine's effect on chorea to justify not approving the application?

Committee Discussion:
Overall, the committee agreed that the findings on the secondary outcomes by themselves do not raise sufficient concern about the utility of tetrabenazine's effect on chorea to justify not approving the application. The committee consensus was that the benefit from the Total Chorea Scale is an accurate measure of an improvement in chorea and that the chorea scores indicate that the drug offers valuable benefit. Although the study (004) is small and data do not show an improvement in function or cognition (and in some cases a numerical superiority in favor of placebo), the statistics supporting a benefit in chorea are strong. The committee also suggested that the instrument used to detect overall functional improvement may not be sensitive or valid and that the instrument itself may need improvement in order to accurately measure functional gain. For these reasons, the committee vote was a unanimous 'no', indicating that there was not sufficient concern to justify not approving the application.
(See Transcript for Complete Discussion)

Yes: 0 **No: 12** **Abstain: 0**

2. If not, is the panoply of adverse effects associated with tetrabenazine use sufficient to justify not approving the application? When considering this question, we are particularly interested in hearing the committee's views about whether or not a dosing regimen can be identified that would provide a benefit on chorea without an unacceptable risk of adverse events. Failing this, we would be interested in hearing the committee's views about any maneuvers that might mitigate these risks sufficiently to justify approval (e.g., reducing the dose, discontinuing the drug, instituting concomitant treatments [e.g., antidepressant therapy]). Further, we are also interested in the committee's views of the aforementioned Agency concerns that it might be difficult for the practitioner to discern if clinical worsening in various areas (e.g., cognition, depression, etc.) is drug related or not, with the possibility that, if drug related, the adverse events could become severe and/or irreversible.

Committee Discussion:
The committee agreed that the panoply of adverse events associated with tetrabenazine use is not sufficient to justify not approving the application. Several suggestions to the dosing regimens were mentioned including using the lowest effective dose for control of the symptoms. The committee also expressed the importance of educating prescribers on detection of differences between adverse events and side effects of tetrabenazine use and progression of symptoms of Huntington's disease (e.g., cognitive loss, extrapyramidal symptoms, and depression). The committee also suggested that advocacy groups in close association with patients and families work with the pharmaceutical companies in post-marketing studies. (*See Transcript for Complete Discussion).*

Yes: 0 **No: 11** **Abstain: 0**

3. If the committee determines that, for any reason, the application should not be approved, what studies (if any) could the sponsor perform to establish the necessary substantial evidence of effectiveness and/or safety in use?

This question was void as the committee unanimously agrees to approve the application. *(See Transcript for Complete Discussion)*

4. If the committee determines that the application should be approved, are there any studies that the Sponsor should perform post-approval?

Committee Discussion:
The committee recommended several possible post-marketing studies that should be considered. One recommendation was a registry to monitor the effects of the treatment on cognitive decline, depression, and suicidal ideation; they pointed out that functional outcomes would certainly be warranted. The committee further recommended studies that would assess the potential for drug-drug interactions. Although the committee felt that a prospective randomized trial against placebo would not be practical once the drug is approved, it might be possible to conduct a randomized drug withdrawal study with blinded evaluations to assess the impact on functional abilities. Finally, the committee suggested that a dose response study for an effect on QTc interval should also be considered.

(See Transcript for Complete Discussion)

The meeting was adjourned at approximately 4:15 p.m. on December 6, 2007.

These summary minutes for the December 6, 2007 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on .

I certify that I attended the December 6, 2007, Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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Darrell Lyons, B.S.N
Designated Federal Officer

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Larry B. Goldstein, M.D.
Acting Chair, PCNS