Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antiviral Drugs Advisory Committee Meeting April 24, 2007

Topic:

The committee discussed new drug application (NDA) 022-128, maraviroc 150 and 300 milligram tablets, Pfizer, Inc., proposed for the treatment of antiretroviral-experienced patients with chemokine (c-c motif) receptor 5 (CCR5)– tropic human immunodeficiency virus (HIV).

These summary minutes for the April 24, 2007 meeting of the Antiviral Drugs Advisory Committee were approved on May 4, 2007.

I certify that I attended the April 24, 2007 meeting for the Antiviral Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Cicely Reese, Pharm.D.

_____/s/_____
Lynn A. Paxton, M.D., M.P.H.
(Acting Chair)

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The following is an internal report which has not been reviewed. A *verbatim* transcript will be available in approximately four weeks, sent to the Division and posted on the FDA website at:

http://www.fda.gov/ohrms/dockets/ac/cder07.htm#AntiviralDrugs

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

Prior to the meeting, the members and the invited temporary voting members had been provided the background material from the FDA. The meeting was called to order by Lynn A. Paxton, M.D., M.P.H. (Acting Committee Chair); the conflict of interest statement was read into the record by Cicely Reese, Pharm.D. (Designated Federal Officer). There were no open public hearing speakers. There were approximately 220 in attendance.

Attendance:
Antiviral Drugs Advisory Committee Members Present (Voting):
Lynn A. Paxton, M.D., M.P.H. (Acting Chair), Janet W. Andersen, Sc.D., Peter L. Havens, M.D., M.S., Maribel Rodriquez-Torres, M.D.

Antiviral Drugs Advisory Committee Temporary Voting Members:
Barbara D. Alexander, M.D., Cynthia Gibert, M.D., Robert M. Grant, M.D., M.P.H.,
Craig W. Hendrix, M.D., Ian M. McGowan, M.D., Ph.D., Sheila Weiss-Smith, M.D., Robert Yarchoan, M.D.

Antiviral Drugs Advisory Committee Patient Representative (Voting):
Lynda Dee, J.D.

FDA Participants at the Table:
Edward M. Cox, M.D., M.P.H., Debra Birnkrant, M.D., Katherine Laessig, M.D., Pravin Jadhav, Ph.D.,
Lisa Naeger, Ph.D., Scott Proestel, M.D.

Members Not Present
Gail J. Demmler, M.D., Robert J. Munk, Ph.D. (Consumer Representative); Eugene Sun, M.D. (Industry Representative –unable to attend at last minute)

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Agenda Proceedings

Opening Remarks	**Lynn A. Paxton, M.D., M.P.H.** Acting Chair, Antiviral Drugs Advisory Committee
FDA Introductory Remarks	**Katherine Laessig, M.D** Medical Team Leader, Products, CDER, FDA

Applicant Presentation

Introduction, Background and Overview of Maraviroc	**Michael Dunne, MD** Therapeutic Area Head, Infectious Diseases, Pfizer
Clinical Efficacy	**Howard Mayer, MD** Global Clinical Leader, Pfizer
Safety and Toleration	**Steve Felstead, MB ChB** Maraviroc Team Leader, Pfizer
In Vitro and In Vivo Tropism and Resistance Evaluation	**Mike Westby, PhD** Virology Team Leader, Pfizer
Medical Need and Place in HIV Armamentarium	**Dan Kuritzkes, MD** Brigham and Women's Hospital, Boston
Conclusions	**Mike Dunne, MD**

FDA Presentation

Clinical Efficacy and Safety	**Scott Proestel, M.D.** Medical Officer Division of Antiviral Products CDER, FDA
Exposure-Response Modeling	**Pravin Jadhav, Ph.D.** Pharmacometrician/Clinical Pharmacologist Office of Clinical Pharmacology CDER, FDA
Tropism and Resistance	**Lisa Naeger, Ph.D.** Clinical Virologist Division of Antiviral Products CDER, FDA

Clarifications / Questions

Lunch

Discussion / Questions

Adjournment

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Discussion Questions

1. **Do the safety and efficacy data presented support accelerated approval of maraviroc for treatment-experienced HIV-1 infected patients with CCR5-tropic virus?**

   If not, please discuss what additional data are needed to provide sufficient evidence of efficacy and safety.

   If so please, comment on additional data (e.g., patient subgroups, longer term follow-up etc.) that Pfizer should provide post-marketing to further characterize the safety and efficacy profile of maraviroc.

   Yes - 12 No - 0

   The committee agreed that data presented supports accelerated approval with the caveat that future study designs include historically relevant groups, specifically minorities. The committee also recommended post-marketing data collection on viral hepatitis co-infection, pediatrics, immunologic signals, and malignancies to further characterize the safety and efficacy profile of maraviroc.

   (See transcript for complete details)

2. **There have been several safety concerns during the development of all the CCR5 co-receptor antagonists including risk of lymphomas and infection, hepatotoxicity, and tropism switching. Please discuss each of these issues with respect to maraviroc specifically, and provide recommendations for possible product labeling, post-marketing studies or post-marketing risk management strategies.**

   The committee suggested that the question be modified to include either theoretical or potential risk based upon data presented. The committee also recommended including both cardiovascular risk with concomitant vasodilators and hemodynamic instability as additional issues. The committee agreed that there was no evidence presented to suggest an increase in lymphomas and recommended it be categorized as a theoretical risk. Discussion of the theoretical risk of lymphoma led the committee to suggest potential breast cancer risk as a greater concern which should be looked at carefully. Infection was not discussed in detail but was modified by the committee as potential risk. Hepatotoxicity was modified as potential risk and the committee agreed that data are relevant however the cases presented are not necessarily an indication of this potential risk. Additional monitoring of patients receiving concomitant hepatotoxic drugs was also recommended. The committee agreed to discuss tropism switching in question four. Hemodynamic instability was periodically discussed as a major concern and was included as a potential risk with respect to maraviroc. Finally, postural hypotension and the potential for QT prolongation was discussed as a dose limiting toxicity with need for language to be included in product labeling. The issue of post-marketing studies or post-marketing risk management strategies were not addressed in full detail and a committee recommendation was not made.

   (See transcript for complete details)

3. **Do the data support the Applicant's proposed dosing? Please consider the recommended dose in light of the exposure-response modeling.**

   Yes - 12 No - 0

   The committee vote was unanimous on *proposed* dosing. The committee recommended establishing a study design to investigate optimization of dose specifically for individuals with low concentrations (e.g, Cmin< 75). There was concern that the current exposure-response did not include sufficient numbers of historically relevant populations. The substantial food effect on maraviroc concentrations and the possible need for such language in labeling was also suggested.

(See transcript for complete details)

4. **The Monogram Trofile assay was used to screen subjects for enrollment and to monitor subjects for tropism switching. Please discuss how you would recommend assays for tropism testing be used for the management of subjects who might receive maraviroc in clinical practice.**

   The committee was unable to determine a specific recommendation regarding assays for tropism testing but did offer many suggestions. The committee did agree that tropism testing was needed to select patients for treatment with maraviroc and some recommended testing at the time of virologic failure.

   (See transcript for complete details)

5. **Please discuss the impact of the availability of maraviroc on the design of future Phase 3 trials for new antiretroviral agents in the treatment-experienced population and provide recommendations for how those trials should be designed accordingly.**

   (Clarification was made by the FDA whether or not substitution studies be designed in the event that a new drug emerges which appears to be better than maraviroc.)

   After much deliberation, the committee was unable to recommend specific trial designs but offered many suggestions for future consideration.

   (See transcript for full details)

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The Meeting adjourned for the day at approximately 4:35 p.m.
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