Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEETING

June 16, 2003

Marriott Washingtonian Center- Rio
9751 Washingtonian Boulevard, Gaithersburg, Maryland

Members Present (Voting)
Matthew Rudorfer, M.D. (Acting Chair)
Tana Grady-Wilky, M.D.
Richard Malone, M.D.
Irene Ortiz, M.D.

FDA Participants
Russell Katz, M.D.
Judith A. Racoosin, M.D., M.P.H.
Tarek A. Hammad, M.D., Ph.D.

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

Consumer Representative
Jean Bronstein

Consultants to the Psychopharmocologic Drugs Advisory Committee (Voting)
Paul Keck, M.D.
Andrew Leon, Ph.D.
Neal Ryan, M.D.
Philip Wang, M.D.
Sheila Weiss, Ph.D.
Ellen Leibenluft, M.D.

Industry Representative (Non-voting)
Dilip Mehta, M.D., Ph.D.

These summary minutes for the June 16, 2003, meeting of the Psychopharmacologic Drugs Advisory Committee were approved on July 15, 2003.

I certify that I attended the March 16-17, 2000 Psychopharmacologic Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

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

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Matthew Rudorfer, M.D.
Chair

On June 16, 2003, the Psychopharmacologic Drugs Advisory Committee met in open session at the Marriott Washingtonian Center, Grand Ballroom, 9751 Washingtonian Boulevard, Gaithersburg, MD. There were approximately 30 persons in attendance.

The meeting was called to order by Matthew Rudorfer, M.D., Acting Committee Chair, and the conflict of interest statement was read into the record by Anuja Patel, Executive Secretary.

Open Public Hearing

Lynn Goldman, M.D.
Maureen Schweers (National Alliance for the Mentally Ill)

Discussions on the white blood cell (WBC) monitoring schedule for patients being treated long-term with clozapine. Currently, the WBC monitoring schedule is weekly for the first six months of continuous therapy and biweekly thereafter. The committee considered the question of whether the frequency of WBC monitoring can be diminished further following some period of biweekly monitoring.

FDA Presentation

Overview of Issues	Judith A. Racoosin, M.D., M.P.H. Safety Team Leader, Division of Neuropharmacologic Drug Products, FDA

Sponsor Presentations

Novartis Pharmaceuticals Corporation

• Introduction	James Rawls, Pharm. D. Associate Director Drug Regulatory Affairs Novartis Pharmaceuticals Corporation
• Overview of Agranulocytosis	Stanton Gerson, M.D. Chief, Division of Hematology and Oncology Department of Medicine Case Western Reserve University
• Clozaril Registry Data	Vinod Kumar, M.D. Executive Director, Clinical Development and Medical Affairs Novartis Pharmaceuticals Corporation
• Quantitative Analysis of US Data	Lawrence Hauptman, M.D. Director, Drug Regulatory Affairs Novartis Pharmaceuticals Corporation
• Summary and Conclusion	John M. Kane, M.D. Professor of Psychiatry, Neurology and Neuroscience Albert Einstein College of Medicine

FDA Presentation

- Discussion of Selected Safety Data — Tarek A. Hammad, M.D., Ph.D.
  Safety Medical Reviewer,
  Division of Neuropharmacologic
  Drug Products, FDA

Questions to the Committee:

1. Should the frequency of WBC monitoring be further reduced after some duration of biweekly monitoring, and if so, when and what reduced frequency of WBC monitoring would be acceptable?

   The Committee's consensus was that the frequency of WBC monitoring could be reduced at some point following bi-weekly monitoring; however, the members were unsure as to precisely when this change could take place. Data from the United Kingdom and Australia, where patients are monitored monthly after some defined point in time, appear to support a change to monthly monitoring since, in these countries, no excessive increase in agranulocytosis rates were seen. Regarding when to effect the change, the committee expressed comfort with recommending that a change could be made following 12 to 24 months of therapy. However, they further agreed that any changes in schedule should only be made for patients whose WBCs have shown to be consistent and within normal range. In spite of their recommendations, the committee acknowledged that if the monitoring interval were expanded to monthly intervals, they would anticipate that there will be an increase seen in the rate of agranulocytosis.

   The Committee suggested that the registries for the marketed generic products (each generic firm operates its own independent registry) and the Clozaril registry be interfaced so that patients who switch to and from generics can be captured in one data base and thus their data integrated.

   - Should white blood cell (WBC) monitoring stop altogether at some time point, and if so when?

     No. The overwhelming consensus of the Committee was that mandatory WBC monitoring should <u>not</u> stop.

   - Should the program be changed overall, e.g., should it become voluntary, as is most advice in labeling regarding monitoring for adverse events?

     No. The overwhelming consensus of the Committee was that the mandatory program should <u>not</u> be changed significantly, nor should it become voluntary. WBC monitoring is essential for patients using clozapine.

2. Should the absolute neutrophil count (ANC) be required as a part of WBC monitoring?

   Yes. The overwhelming consensus of the Committee was that, as is required in the UK, the absolute neutrophil count (ANC) should be a requirement of the monitoring program. The current physician labeling for clozapine requires that an ANC be performed, however, the Clozaril National Registry (CNR) does not capture the results of this testing. The consensus of the Committee was that this data be added to the Registry.

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