

**Food and Drug Administration
Center for Drug Evaluation and Research**

**SUMMARY MINUTES OF
PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY
COMMITTEE MEETING**

September 24, 2003
Memantine HCl

Holiday Inn
Versailles Ballrooms, 8120 Wisconsin Avenue, Bethesda, MD

Members Present (Voting)

Claudia H. Kawas, M.D., Chair
Jerry S. Wolinsky, M.D.

FDA Participants

Robert Temple, M.D.
Russell Katz, M.D.
Armando Oliva, M.D.
Ranjit Mani, M.D.

Executive Secretary

Anuja M. Patel, M.P.H.

Consultants to the PCNS Drugs Advisory Committee (Voting)

Steven Ebert, Pharm. D. (Consumer Representative)
Gerald van Belle, Ph. D.
Mary Ganguli, M.D., M.P.H.
Karl D. Kieburtz, M.D., M.P.H.
Jorge C. Kattah, M.D.
Roger J. Packer, M.D.

Industry Representative (Non-Voting)

Daniel Azarnoff, M.D.

These summary minutes for the September 24, 2003, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee were approved on _____.

I certify that I attended the September 24, 2003, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

_____/S//_____
Anuja M. Patel, M.P.H.
Executive Secretary

_____/S//_____
Claudia Kawas, M.D.
Chair

On September 24, 2003, the Peripheral and Central Nervous System Drugs Advisory Committee met in open session at the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland. There were approximately 300 people in attendance.

At 8:00 a.m., the meeting was called to order by Claudia Kawas, M.D., Chair. This was followed by the conflict of interest statement, read by Anuja M. Patel, M.P.H., Executive Secretary, and the introduction of meeting participants.

Open Public Hearing Speaker:

- Barry A. Cooper, MHA
Companion Care Association, Inc.

Issue:

Discussions on new drug application (NDA) 21-487, memantine hydrochloride, Forest Laboratories, Inc., indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

FDA Presentation

- Opening Remarks and Overview of Issues
Russell Katz, M.D.
Director, Division of Neuropharmacologic Drug Products, FDA

Sponsor Presentation

Forest Laboratories Incorporated

- Introduction and Memantine Overview
Lawrence Olanoff, M.D., Ph.D.
Executive Vice President,
Forest Laboratories Incorporated
- Memantine Pharmacology
J. Timothy Greenamyre, M.D., Ph.D.
Professor, Neurology
Co-Director, Center for Neurodegenerative Disease,
Emory University
- Efficacy Data
Lon S. Schneider, M.D.
Professor of Psychiatry, Neurology, and Gerontology,
University of Southern California,
Keck School of Medicine
- Memantine Safety and Tolerability
Jeffrey Jonas, M.D.
Safety Vice President, CNS
Forest Research Institute
- Summary and Risk/Benefit
Steven T. DeKosky, M.D.
Professor and Chair, Department of Neurology;
Director, Alzheimer's Disease Research Center,
University of Pittsburgh

FDA Presentation

Ranjit Mani, M.D.
Medical Reviewer, Division of Neuropharmacological Drug Products, FDA

Questions for Advisory Committee

1. Has the population for which the use of memantine is proposed been adequately identified in the studies included in this application?

YES – 8

No – 0

The Committee felt that the population was adequately identified given that the population was defined by using the Mini-Mental State Exam (MMSE) scale. Individual members expressed concern over certain limitations of individual studies such as the body of evidence on severe Alzheimer's disease patients in the Latvian study was small and the arbitrariness of the scales applied to each study.

2. Are the designs of the key studies in this application adequate for evaluating the efficacy of memantine for the proposed indication?

YES – 8

No - 0

The Committee felt that the key studies in this application are adequate for evaluating efficacy of memantine for the proposed indication. However, individual members expressed concern in identifying the key studies. The Committee felt that the US studies were the key studies. The Committee felt that the Latvian study may or may not have been adequate in assisting the Committee in evaluating the issues related efficacy of memantine.

- In particular, are the instruments used to evaluate efficacy in these studies appropriate for patients with moderate-to-severe Alzheimer's Disease?

YES – 8

No -0

The Committee felt that the instruments were reasonably appropriate for population studied in that they were state of the art at the time of the studies. However, individual members expressed the opinion that the instruments should be improved in the future. Two global measures that are similar for the measure being studied should not be used; rather, a cognitive measure and a global measure should be applied in the future. In the long-term, more appropriate measures such as combining two different measures as oppose to similar measures should be explored.

3. Has substantial evidence of the effectiveness of memantine for the proposed indication been demonstrated by the studies included in this application?

YES – 8

No –0

The Committee felt that the evidence of the effectiveness of memantine for the proposed indication has been demonstrated by the studies included in this application. The data should be further studied. Individual members expressed concern over the varying evidence of effectiveness and small effect size among the studies.

4. Has substantial evidence of the safety of memantine for the proposed indication been demonstrated by the studies included in this application?

YES – 8

No -0

The Committee felt that evidence of the safety of memantine for the proposed indication was demonstrated. However, individual members expressed concern related to the long-term issue when applied to larger population, drug interactions, and data shown in animal models. Additional information for combining cholinesterase inhibitors with memantine should be explored in the future.

Committee Overview:

The Chair stated, prior to adjourning, that although the votes were unanimous, several members of the Committee expressed concerns and reservations. Members expressed difficulty in identifying the key studies in evaluating efficacy of memantine; furthermore, members suggested that more appropriate measures such as combining two different measures as oppose to similar measures should be explored when evaluating efficacy in Alzheimer's disease patients. Overall, additional data should be collected regarding the long-term effectiveness of memantine when applied to a larger population and its drug interactions should be further explored.

Following completion of discussion of the questions, the committee adjourned at approximately 4:00 PM.

Prepared by:**Anuja M. Patel, M.P.H.****Executive Secretary****Peripheral and Central Nervous System Drugs Advisory Committee**