Food and Drug Administration
Center for Drug Evaluation and Research

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

September 25, 2003

Provigil®

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.
John Feeney, III, M.D.
Norman Hershkowitz, M.D., Ph.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.
Jorge C. Kattah, M.D.
Emanuel J. Mignot, M.D., Ph.D
Lois E. Krahn, M.D.
David Neubauer, M.D.

Industry Representative (Non-Voting)
Daniel Azarnoff , M.D.

These summary minutes for the September 25, 2003, meeting of the Peripheral and Central Nervous System Drugs Advisory Committee were approved on _____.

I certify that I attended the September 25, 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 25, 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 200 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:

- Richard Gelula, MSW
  Executive Director, National Sleep Foundation

- Christin Engelhardt
  Executive Director, American Sleep Apnea Organization

Issue:
Discussion on supplementary new drug application (SNDA 20-717 /S-008) Provigil (modafinil) Tablets, Cephalon, Inc., indicated for use to improve wakefulness in patients with excessive sleepiness associated with disorders of sleep and wakefulness.

FDA Presentation

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

Sponsor Presentation

• Introduction	Lesley Russell, MBChB, MRCP Vice President, Clinical Research, Cephalon Incorporated
• Review of Excessive Sleepiness	Thomas Roth, Ph.D. Division Head, Sleep Disorders and Research Center, Henry Ford Hospital
• Overview of Efficacy	Rod Hughes, Ph. D Senior Director, Clinical Research, Cephalon Incorporated
• Overview of Safety	Gwendolyn Niebler, D.O. Senior Director, Clinical Research, Cephalon Incorporated
• Conclusion	Lesley Russell, MBChB, MRCP Vice President, Clinical Research, Cephalon Incorporated

Questions for Advisory Committee

1. Using the International Classification of Sleep Disorders (ICSD), the sponsor has defined "Disorders of Sleep and Wakefulness Associated with Excessive Sleepiness." Does the Committee agree with this designation?

   Yes – 7 No- 0 Abstain- 1

   One member of the Committee deferred to the sleep experts.

2. The sponsor believes that the above group can be divided into three categories, based on the presumed cause of the excessive sleepiness. The categories are: sleep-wake dysregulation, sleep disruption, and circadian misalignment. Does the Committee agree with this classification?

   Yes – 7 No- 0 Abstain- 1

   One member of the Committee deferred to the sleep experts.

3. Does the Committee agree that the disorders studied by the sponsor, narcolepsy, obstructive sleep apnea (OSAHS), and shift work sleep disorder (SWSD), are representative of the three categories described above?

   Yes - 3 No- 5

   Although the some members of the committee agree with the three categories on presumed cause of excessive sleepiness is an acceptable division for some, the Committee felt that the definition of "representative" in the question was unclear. The Committee was told that "representative" in this case meant that if the drug works in one of the diseases in the category, could we assume that it works in all of them. There are times when one can make this assumption, such as when you know that the diseases share pathophysiology and thus are likely to respond to the same treatments. In this case, those who voted "no" felt that we could not make this assumption. Additionally, individual members felt that the information provided by the Sponsor was not enough information in terms of efficacy or safety of Provigil for other diseases within the three subcategories.

   One member of the committee voted yes, provided that "representative" was substituted with "convenience samples".

4. Does the Committee agree that the sponsor has submitted substantial evidence of effectiveness for the indication, "…for the treatment of excessive sleepiness associated with disorders of sleep and wakefulness…"?

   Yes - 4 No- 4

   Members expressed their reservations such as the global nature of the indication given by the Sponsor. Some felt that it is difficult to highlight these three disorders and say that it is representative of all the disorders.

5. Has the sponsor demonstrated that Provigil can be used safely for this broad indication?

   Yes - 5 No- 2 Split-vote- 1

   One member of the committee felt that the sponsor demonstrated Provigil can be used safely for the broad indication for narcolepsy and shift work sleep disorders but not for sleep apnea patients. The member suggested that additional information be collected in regards to safety in sleep apnea patients.

If the Committee does not vote "yes" on questions 1-5:

1. Has the Sponsor provided substantial evidence of effectiveness to support the use of Provigil in the treatment of excessive sleepiness in patients diagnosed with OSAHS?

   Yes - 8 No- 0

   The vote was unanimous; however, some members expressed reservations provided that Provigil be used as adjunctive therapy to C-PAP (Continuous Positive Airway Pressure).

2. Has the Sponsor provided substantial evidence of effectiveness to support the use of Provigil in the treatment of excessive sleepiness in patients diagnosed with SWSD?

   Yes - 6 No- 2

   Members expressed their opinion that this drug is the treatment of a symptom not on the elimination of a disease and given the fact the drug has a similar effect on that symptom for the other diseases discussed. The committee suggested that strong labeling measures be taken by the Food and Drug Administration to include the sleep apnea and shift work sleep disorders (SWSD).

   Committee members that voted "no" were concerned that the criterion is for two independent studies and the Committee was presented one. Furthermore, the conceptual issues of exactly what constitutes the SWSD as oppose to those individuals who are doing shift work and experiencing sleepiness; and also the effectiveness is questionable patients who are still in a range of profound sleepiness.

Following completion of discussion of the questions, the committee adjourned at approximately 2:30 PM.

Prepared by:

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