

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 3, 2006

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: March 23, 2006 Meeting of the Psychopharmacologic Drugs Advisory Committee
(PDAC)

TO: Members, PDAC

This one-day PDAC meeting will focus on NDA 20-717/S-019 for modafinil in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Modafinil is marketed as Provigil to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. It is a schedule 4 drug. The recommended dose in these disorders in adults is 200 mg/day. Its pharmacological mechanism in improving increased wakefulness is not understood. This supplement provides data in support of a claim for the safety and short-term effectiveness of modafinil in ADHD in children and adolescents, at doses of 340 mg/day (in patients < 30 kg) and 425 mg/day (in patients > 30 kg).

This supplemental NDA for modafinil was submitted 12-20-04, and an approvable letter was issued 10-20-05. Although the division issued an approvable letter, we raised a concern about three types of adverse events: (1) serious skin rashes; (2) psychiatric adverse events, and (3) three patients with transaminase elevations, and we asked for additional information pertinent to such events. The sponsor has provided an 11-21-05 response to our approvable action that includes responses to all of our requests.

The clinical reviewer for the original supplement was Glenn Mannheim, M.D., who concluded that, because of what he considers serious risks with this drug, modafinil should not be approved for ADHD. The Division of Psychiatry Products has not yet reached a final decision on this application, and seeks the advice of the PDAC before reaching a conclusion.

The Division's background package includes the following background information:

- Dr. Mannheim's original clinical review
- An approvable memo by Paul Andreason, M.D., Acting Deputy Director
- An approvable memo by Thomas Laughren, M.D., Division Director
- October 20, 2005 Approvable Letter
- A consultative review of the serious rashes by Markham Luke, M.D., a dermatologist from the Division of Dermatological and Dental Drug Products

-A consultative review of the serious rashes, including new information provided in the response to the approvable action, by Joseph Porres, M.D., a dermatologist from the Division of Dermatological and Dental Drug Products

-The sponsor's proposed labeling (package insert) for this product.

After you have heard all the findings and arguments, we will ask you to vote on two questions:

1. Has modafinil been shown to be effective for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents?
2. Has modafinil been shown to be acceptably safe in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents?

In addition to your deliberations on the above two questions, we ask for comment on additional questions, assuming modafinil were to be considered for approval:

- What kind of a risk management plan should be implemented with regard to the signal for serious skin rashes with this drug in the ADHD program?
- How should the concern about serious skin rashes be addressed in product labeling (you have been provided our labeling proposal in the approvable letter and also the sponsor's currently proposed labeling)?
- Should there be a requirement for a post-marketing study(ies) to better understand the serious skin rashes, and what type of study(ies) might be considered?

cc:

HFD-130/TLaughren/PAndreason/SPlayer

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