

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

DATE: October 19, 2005

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

SUBJECT: Recommendation for Approvable Action for Modafinil tablets for ADHD in
children and adolescents

TO: File NDA 20-717/S-019
[Note: This overview should be filed with the 12-20-04 original submission of
this supplement.]

1.0 BACKGROUND

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. 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 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).

We held an EOP2 meeting with the sponsor on 8-23-03 and reached agreement on most issues for this planned program. We held a preNDA meeting with the sponsor on 7-8-04. In this meeting, we reached agreement that the 4-month safety update would include data from approximately 175 patients treated for at least 12 months.

Since this application involved new tablet strengths for modafinil, there was a need for reviews by chemistry (Sherita McLamore, Ph.D.), biopharmaceutics (Christine Garnett, Ph.D.), and pharmacology/toxicology (Aisar Atrakchi, Ph.D.). The primary review of the efficacy and safety data was done by Glenn Mannheim, M.D., from the clinical group. Tristan Massie, Ph.D., from the biometrics group, also reviewed the efficacy data.

The studies supporting this supplement were conducted under IND 59,661, and this supplement was submitted on 12-20-04.

DNDP (before the split into Neurology and Psychiatry) decided not to take modafinil for ADHD to the Psychopharmacological Drugs Advisory Committee (PDAC), at least in this initial review cycle. We may reconsider this decision once the sponsor responds to our action letter.

2.0 CHEMISTRY

Modafinil dose strengths for the adult indications are 100 and 200 mg. Cephalon developed new dosage strengths for the new ADHD indication: 85; 170; 255; 340; and 425 mg.

The sponsor's rationale for these new strengths was the need to have somewhat smaller tablet sizes, given the pediatric population, and at the same time accommodate a higher active drug load. The chemistry group has deemed the new tablets acceptable, and has recommended an approvable action, with several deficiency comments for the letter. They have proposed minor changes to the sponsor's proposed label.

The sponsor has also proposed a new brand name, i.e., "SPARLON", in order to distinguish this product from Provigil. Although DMETS in general recommends against dual names for the same product, they consider this proposed name acceptable if we decide dual names are acceptable. In this event, DMETS has proposed a number of comments for the sponsor for a risk minimization program. Although I also, in general, would prefer that companies not utilize different names for the same product, there are multiple examples where DNDP and other divisions have permitted dual names. Thus, it is difficult for DPP to justify not permitting dual names in this setting. We will, however, convey DMETS's recommendations for a risk minimization program.

3.0 PHARMACOLOGY

Earlier in drug development, the sponsor was asked to conduct juvenile animal studies, and they conducted 3-month studies in rats and dogs. Dr. Atrakchi reviewed these studies even prior to the submission of this supplement, and these studies did not reveal any specific concerns. However, Dr. Atrakchi is concerned about the greater relative and absolute exposure to the sulfone metabolite in children compared to adolescents and adults (see 4.0, Biopharmaceutics). Based on these concerns, Dr. Atrakchi has asked for additional tox testing of the sulfone metabolite. It is true that exposures to the sulfone metabolite have been relatively low in animal studies compared to human studies, both adult and children, but especially in children (see Dr. Rosloff's memo). However, as Dr. Rosloff points out, it is often the case that not all circulating species in animal studies cover human exposures to the same extent, and we do not generally require additional testing if MTDs were used, as was the case here (except for the 1 month rat study specifically of the sulfone metabolite). Dr. Rosloff feels that exposures to the sulfone metabolite in animal studies were not sufficiently insignificant to justify asking for additional animal studies, and in fact, the toxicity to the sulfone metabolite appeared to be similar to that

seen for the parent. Thus, Dr. Rosloff does not feel that there is a sufficient basis to request additional animal toxicity testing of the sulfone metabolite, and I agree.

4.0 BIOPHARMACEUTICS

The sponsor was required to characterize the pharmacokinetics of the new tablets in pediatric patients, and OCPB is satisfied that they have adequately accomplished this characterization. They have granted a biowaiver for the 170, 255, and 340 mg tablets. OCPB has proposed a number of comments for labeling and also comments to convey in an approvable letter. They have requested that the sponsor provide justification for the proposed dissolution method (as a phase 4 commitment) and they have recommended that the sponsor assess the potential for modafinil to induce CYP2C8.

It should be noted that the modafinil sulfone metabolite accumulates to a greater extent in children than in adolescents and adults. In children, the AUC of the sulfone metabolite is up to 3 times that of parent drug, while in adults the AUC of the sulfone metabolite is only about ½ that of parent drug. In terms of absolute levels, the AUC for the sulfone metabolite in children was observed to be up to 8 times greater than the AUCs for this metabolite seen in adults. Although the toxicology profile of this metabolite is similar to the parent, OCPB has raised a concern about the induction potential of this metabolite. Labeling will address this concern about a possibility of greater induction of 1A2, 2B6, and 3A4 in children and also a possibly greater inhibitory effect on 2C19. Another concern that has been raised is the possibility of a greater risk of sensitivity reactions to the sulfone metabolite in children (see later under discussion of serious rashes).

5.0 CLINICAL DATA

5.1 Efficacy Data

There were three 7 to 9 week, double-blind, placebo-controlled, parallel group RCTs in children and adolescents aged 6 to 17 who met DSM-IV criteria for ADHD. These patients were at least moderately ill (86% moderately to markedly ill, and 14% severely ill). The distribution of ADHD subtypes were as follows: inattentive (30%); hyperactive (5%); combined (65%). Patients were predominantly male (71%) and Caucasian (76%). About 2/3 were < 12 years of age. The primary assessment was the ADHD-RS-IV (school version), and the primary outcome was change from baseline on this measure.

Two of the trials (309 & 311) were identical flexible dose studies (patients were mostly pushed up to the maximum permitted dose of 425 mg/day). The third trial was fixed dose (340 mg/day for patients < 30 kg and 425 mg/day for patients ≥ 30 kg). [Note: Phase 2 study 207 compared 5 different doses, and established that only the higher doses (340 and 425 mg/day were effective, and this is the reason the phase 3 trials focused on these higher doses.)]

All 3 trials were highly significant ($p < 0.001$) in favor of modafinil, and both the clinical and statistical reviewers agreed that these studies provided support for the short-term efficacy of modafinil in pediatric ADHD.

5.2 Safety Data

5.2.1 Focus of My Comments on the Safety of Modafinil in Pediatric ADHD

Dr. Mannheim has recommended a non-approval action based on concerns about the safety of this product in pediatric ADHD. There are several areas of concern that Dr. Mannheim identifies, including the following:

- Serious rash
- Possible Reye's syndrome
- Hepatotoxicity
- Serious psychiatric adverse events
- Leukopenia
- Peptic ulcer disease
- Weight effects

A central element of Dr. Mannheim's concern appears to be the finding of a greater extent of accumulation of the sulfone metabolite of modafinil in children weighing < 30 kg compared to heavier individuals [see Biopharm (4.0)]. As noted, the general animal toxicology profile for the sulfone metabolite is similar to that for the parent.

5.2.2 Clinical Data Sources for Safety Review

The clinical trials safety data for these supplements included safety data from a total of $n=933$ pediatric patients exposed to modafinil across 8 trials. These were 4 clinical pharmacology trials (1024 & 113 were BE/BA studies; 207 and 213 were phase 2 efficacy trials), 3 phase 3 safety and efficacy trials (309, 310, and 311), and 1 ongoing longer-term trial (312). The common adverse event profile was derived from the three phase 3 efficacy and safety studies (420 exposed to modafinil and 213 exposed to placebo).

5.2.3 Adverse Event Profile for Modafinil in Pediatric ADHD

There were no deaths in the clinical trials in ADHD for modafinil. Adverse dropouts overall in the short-term phase 3 trials occurred at a rate of 5% for drug and 3% for placebo. The most common reasons for dropouts related to modafinil were insomnia, abdominal pain, and emotional lability. Adverse dropouts deemed common and drug-related ($\geq 5\%$ and $>$ placebo) included insomnia, headache, anorexia, abdominal pain, fever, and nervousness. However, of these, the only 2 that were meaningfully different from placebo were insomnia and anorexia (i.e., a profile similar to that seen with other ADHD products). [Note: The incidence of insomnia for modafinil (27% for modafinil vs 4% for placebo) is higher than is usually seen for ADHD trials,

however, this is an event that can be labeled, and managed, if it persists, by switching to another drug.] The sponsor notes further that, for insomnia and anorexia, the rates for these events declined over time, in part due to dropouts due to these events and in part likely due to adaptation in those remaining on drug. These declines could also be due to decreased reporting by patients and investigators over time, rather than to an actual decrease in the occurrence of the events. Given the difficulty in interpreting these apparent declines over time, we will not permit these ambiguous findings to be included in labeling. Evaluation of laboratory, vital signs, and ECG data based on mean changes for drug and placebo groups in the controlled phase 3 trials did not reveal any drug-related changes not already recognized for modafinil. In this pediatric group, there were no drug/placebo differences in vital signs or ECGs. There was a tendency to weight decrease associated with drug in the short-term trials (mean decrease of 0.7 kg for modafinil and 1.0 kg increase for placebo). There were no clinically meaningful drug-related changes in neutrophils or total WBC counts. The only drug-related laboratory changes observed were very modest increases for alkaline phosphatase and GGT, similar to what was seen in adults, and a modest decrease for uric acid. There were no transaminase increases.

5.2.4 Special Safety Concerns for Modafinil in Pediatric ADHD

5.2.4.1 Serious Rash

There were 3 cases of clinically important rash among 933 patients exposed to modafinil in this program (Dr. Andreason and I did not learn about these until very late in the review cycle, i.e., mid-Sept, 2005).

-One of these was a 7 year old male (Study 311/Pt 062338) who was noted to have a sore throat, fever and mild rash by day 16 of treatment with modafinil 340 mg/day.

Amoxicillin was started on day 17, but apparently was limited to a single dose. The modafinil was also stopped by day 17. By day 19, the rash was spreading, and continued to progress, with blistering, peeling, and mucosal involvement (lips and urethral meatus). A dermatologist made a diagnosis of Stevens-Johnson. The rash appeared to resolve by day 30. No skin biopsy results were reported. Our consulting dermatologist, Dr. Markham Luke, suggested trying to obtain RAST testing for penicillin allergy for this patient. Given the limited data available, he feels that modafinil cannot be ruled out as a possible cause of this serious event.

-A second case involved an 11 year old female (Study 207/Pt 315) with a maculopapular rash that developed on day 4 of treatment. The patient was treated with diphenhydramine, but the rash worsened and the patient was hospitalized on day 15. A dermatologist considered this to represent a morbilliform rash and treated it with an antihistamine. It resolved within a week. Dr. Luke does not consider this case to be EM/ST.

-A third case involved an 8 year old male (Study 213/Pt 180004) with mild fever, rash on the cheeks and severe blisters on the lips by day 14 of treatment. Modafinil was stopped at this point, and the rash resolved. Dr. Luke feels there is too little information to interpret this case.

There were also less significant rashes, and overall, the incidence of rash in the three phase 3 trials was 4% for modafinil and 2% for placebo.

We are also aware of 5 AERS reports of either erythema multiforme or Stevens-Johnson in adults treated with modafinil.

Comment: Finding even a single case of Stevens-Johnson in a small controlled trials experience is of concern, given how rare this event is as a background event. The finding of 5 AERS reports of either erythema multiforme or Stevens-Johnson adds to the concern that the Stevens-Johnson case in the controlled trial may have been related to modafinil use. We will ask the sponsor to obtain whatever additional information might be available for this case, e.g., a skin biopsy if obtained and RAST testing for penicillin allergy, if feasible. The presence of excess levels of the sulfone metabolite in children compared to adolescents and adults suggests the possibility of sulfone allergy as a possible mechanism for this event, and we will ask the sponsor to consider further evaluation of this possibility. We will also ask the sponsor to consider getting their own expert dermatological consultation on these cases. Finally, we will ask that they propose labeling to appropriately warn of the risk of serious skin rash. In the absence of a better understanding of these events, I consider a warning statement to be the appropriate level for this event, along with clear advice to seek medical attention at the first sign of a rash.

5.2.4.2 Possible Reye's Syndrome

Late in the review cycle, we learned of a case of what appeared to be Reye's syndrome in a 6 year old male who had been taking modafinil in a trial of excessive daytime sleepiness in children (Note: This AE came from a different program, thus, did not occur among the 933 exposures in the ADHD program). He had been taking modafinil for about 11 days, and was on a dose of 400 mg/day, when he began experiencing nausea, vomiting, pharyngitis and fever. He was subsequently hospitalized and worked up for possible Reye's syndrome, although there was no history of ASA intake. He subsequently experienced delirium, hallucinations, and seizures, and was found to have elevated ammonia levels. He was not reported to have elevated transaminases, however, it was difficult to get information from the hospitalization. He ultimately recovered. This case was reviewed, to the extent possible given the difficulty in getting information (the family was uncooperative) by Dr. John Senior, and he concluded that it was most likely a Reye's case, and also concluded that it was not likely related to modafinil use. He further concluded that there was no basis for a labeling recommendation to monitor serum transaminases or close followup for this type of event. I agree.

5.2.4.3 Hepatotoxicity

As noted above, the only drug-related laboratory mean changes indicative of hepatic effects observed in a pool of the 3 efficacy trials were very modest increases for alkaline phosphatase and GGT, similar to what was seen in adults, and no transaminase increases. An assessment for transaminase outliers (> 3XULN on ALT or AST) in these 3 studies revealed no events for AST

and roughly the same proportions for both groups for ALT [3/420 (0.7%) for modafinil and 1/213 (0.5%) for placebo].

Although the controlled trials data did not reveal a signal for drug-related mean increase in transaminase values or in drug-related outliers, there were 3 modafinil-treated patients who had transaminase increases of concern but insufficient other information to further assess the significance of these changes:

-Patient 056003: This was a 9 year old male who developed fever, generalized hives, and vomiting on day 13 of modafinil treatment. Treatment was stopped, but on day 14 he was noted to have an ALT of 517 U/L and AST of 409 U/L. These levels returned to normal by days 23 and 35 respectively.

-Patient 63329: This was a 17 year old male with an ALT of 453 U/L and AST of 269 U/L.

-Patient 006120: This was a 9 year old male with an AST of 262 U/L.

We will ask the sponsor to determine if bilirubin values were obtained for these patients, and if so, to provide these and any other relevant clinical data that would help in determining the seriousness of these cases.

5.2.4.4 Serious Psychiatric Adverse Events

Although the sponsor's 2% adverse event table (Table 2 in the proposed label) does not identify any psychiatric events as showing an excess for drug compared to placebo, it is striking when assessing dropouts for psychiatric adverse events that almost all of the dropouts for certain psychiatric adverse events occurred in modafinil-treated patients. These events included suicidal ideation, agitation, depression, and psychosis. In addition, it appears that, in certain instances, the coding of events leading to discontinuation incorrectly classified the event. For example, patient 14016 in study 311 was categorized as a dropout for "personality disorder" when the behavior described as leading to discontinuation involved placing a rope around his neck. This example and others raises a concern about the coding of psychiatric adverse events in this program. In general, there have been recent concerns raised about psychiatric adverse events occurring in association with drugs used to treat ADHD. In fact, the agency sent request letters on 9-15-05 asking sponsors of approved ADHD products and several drugs under development for ADHD to re-examine their controlled trials databases for psychiatric adverse events (Cephalon received such a request for modafinil trials in ADHD). Given this concern, we will ask that, as part of the response to this action letter, the sponsor complete this requested search for their modafinil trials, and in addition, that they conduct appropriate analyses of the data accumulated in this search for psychiatric adverse events. As part of this exploration for psychiatric adverse events, we will ask that they re-consider the coding of psychiatric adverse events in their program to ensure that this was done appropriately.

5.2.4.5 Leukopenia

The early trials with modafinil in pediatric patients there was a suggestion of transient decreases in WBC and ANC counts, and this has not been seen in adults. Similar clinically insignificant mean decreases were seen in the later pediatric trials as well, but there were no drug/placebo differences in clinically important changes in ANC. There was also no signal of a greater incidence of infections in modafinil-treated patients. Two AERS searches for neutropenia in pediatric patients exposed to modafinil also revealed no signal for agranulocytosis. In my view, this concern has been adequately addressed in the sponsor's proposed labeling.

5.2.4.6 Peptic Ulcer Disease

Dr. Mannheim raises a concern about 2 cases of dyspepsia in modafinil-exposed patients, including 1 positive for *H. pylori*. This is in fact not that uncommon in pediatric patients and I think this has been adequately addressed in the sponsor's proposed labeling.

5.2.4.7 Weight Effects

As noted above, there was a tendency to weight decrease associated with drug in the short-term trials (mean decrease of 0.7 kg for modafinil and 1.0 kg increase for placebo). An alternative approach to looking at decreased weight is to compare proportions of drug and placebo patients who lost $\geq 7\%$ of body weight (these proportions were 9% and 1% , respectively, for modafinil and placebo in the short-term controlled trials). In my view, this concern has been adequately addressed in the sponsor's proposed labeling (i.e, a Warning statement).

5.2.5 Conclusions Regarding Safety of Modafinil in Pediatric ADHD

I agree with Dr. Mannheim that there are some significant safety concerns with this product in pediatric patients, however, I disagree that these findings should be the basis for a nonapproval action [Note: Thus, I am in agreement with Dr. Paul Andreason, acting deputy director of DPP on this matter.]. I feel that we can request further information and, depending on what is submitted, we may decide to take this application to the PDAC for further discussion.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and more changes will likely be needed once they respond to our information requests.

6.0 WORLD LITERATURE

The sponsor provided a warrant that they reviewed the literature and found no relevant papers that would adversely affect conclusions about the safety of modafinil in the treatment of ADHD.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, modafinil is approved for ADHD only in Mexico.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

DNDP decided not to take this application to the PDAC, however, I will reconsider this decision once the sponsor has responded to our requests for information.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 sites from the studies supporting the efficacy of modafinil in ADHD, and overall, the data from these sites were deemed to be acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have made a number changes to the sponsor's proposed label.

10.2 Approvable Letter

The approvable letter includes our proposed labeling and requests for responses to numerous questions that were raised during the course of the review that the sponsor needs to address in order for us to complete the review of this supplement.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Cephalon has submitted sufficient data to support a potentially approvable action for modafinil in the treatment of ADHD. However, before we can take an approval action, they need to respond to various requests we have made and we need to reach agreement on labeling. We may, in the interim, decide that we need to take this application to the PDAC for further discussion. Thus, we will issue the attached approvable letter along with our proposal for labeling.

cc:
Orig NDA 20-717/S-019 (Modafinil/ADHD)
HFD-130
HFD-130/TLaughren/PAndreason/GMannheim/RTaylor

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/s/

Thomas Laughren
10/20/2005 09:44:02 AM
MEDICAL OFFICER