

MEMORANDUM

DATE: September 8, 2003

FROM: Director
Division of Neuropharmacological Drug Products

TO: Members
Peripheral and Central Nervous Systems Drugs Advisory
Committee

SUBJECT: September 25, 2003 PCNS Advisory Committee Meeting to
Discuss NDA 20-717 for the use of Provigil (modafinil) Tablets in
the treatment of Excessive Sleepiness Associated with Disorders of
Sleep and Wakefulness

As you know, the PCNS Advisory Committee will meet on 9/25/03 to discuss supplemental NDA 20-717, for the use of Provigil (modafinil) Tablets in the treatment of Excessive Sleepiness (ES) Associated with Disorders of Sleep and Wakefulness. This supplement was submitted by Cephalon, Inc., on 12/20/02. Provigil is currently approved to improve wakefulness in patients with excessive daytime sleepiness (EDS) associated with narcolepsy.

The application contains the results of three newly conducted randomized controlled trials, two in patients with Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS; a disease characterized by collapse of the upper airway during sleep, leading to arousals during, and disruption of, sleep, with resultant ES during the day) and one in patients with Shift Work Sleep Disorder (SWSD; a disturbance in people who work outside normal working hours, resulting in ES at night and poor sleep during the day, and presumably related to a mis-alignment of circadian rhythms and the "normal" work/rest cycle). In addition, the sponsor briefly reports the results of the two trials previously performed in patients with narcolepsy, and which served as the basis for the current approval.

You have already received the briefing document prepared by the sponsor, in which they describe the results of their trials, and in which they present their argument to support their proposed indication. Unfortunately, the Agency reviews of the application are not completed; therefore, we cannot forward to you our independent analyses of the data. However, we have reviewed the sponsor's description of the controlled trial data, and are in general agreement with the results of their analyses.

In this memo, I will briefly review the data, and outline the issues we would like the Committee to discuss at the 9/25 meeting.

As the sponsor describes, they have, in large part related to multiple discussions held with the Division, chosen to evaluate the effects of Provigil on the excessive sleepiness seen in patients with three distinct diseases already mentioned (narcolepsy, OSAHS, and SWSD) as support for their proposed claim. In the first two settings, the excessive sleepiness occurs during daylight hours, and in SWSD, the excessive sleepiness occurs during the hours the subject is supposed to be awake, namely, at night, during what for them is their work time. Based on the trials in these three settings, the sponsor wishes to be granted a general claim for "Excessive sleepiness associated with disorders of sleep and wakefulness".

This proposed general claim, and the approach taken by the sponsor, are the direct results of the sponsor's classification of the various sleep disorders.

As the sponsor notes, the International Classification of Sleep Disorders (ICSD) classifies sleep disorders into four main categories: Dyssomnias, Parasomnias, Sleep Disorders Associated with Mental, Neurologic, or other Medical Disorders, and Proposed Sleep Disorders.

According to the sponsor, the Dyssomnias are disorders of initiation and maintenance of sleep and disorders of excessive sleepiness, or both. The Parasomnias are disorders of arousal, partial arousal, or sleep stage transition; according to the sponsor, these disorders do not give rise to complaints of excessive sleepiness. The third category comprises sleep disorders thought to be secondary to other more primary disorders, and the fourth category comprises disorders that are not yet well characterized.

The sponsor believes that the primary sleep disorders associated with ES can be broken into four categories: those associated with sleep induced respiratory impairment; those associated with movement disorders; those associated with disorders of the timing of the sleep-wake pattern; and those associated with neurologic disorders (see the sponsor's table, page 17 of their briefing document).

The sponsor asserts that the pathophysiology of ES is sleep disruption and increased drive for sleep during wakefulness. Given this view, they believe it is reasonable to classify the four primary categories of sleep disorders associated with ES into three categories, defined by the following primary pathophysiologic mechanisms:

- 1) Sleep-wake dysregulation
- 2) Sleep disruption
- 3) Circadian misalignment

Because of their view that the conditions included in these three groupings all share a common clinical picture (namely evidence of disturbed sleep and an

increased drive for sleep during periods that the subject wishes to be awake), they believe that these disorders can reasonably be considered to be Disorders of Sleep and Wakefulness.

As can be seen in the sponsor's Table 1, page 19, they have subsumed various diagnoses under these three categories. In the first category, Narcolepsy is apparently the most common diagnosis, in the second category, OSAHS is the most common, and in the third category, SWSD is the most common diagnosis. It is for this reason that they have chosen these conditions to study, and these serve as the basis of support for their proposed general claim. The sponsor, therefore, has chosen to support a general claim based on the demonstration of effectiveness in the most common diseases they believe are representative of each of the three categories of pathophysiology that produce ES.

I will very briefly review the primary findings on the three newly performed studies; please see the sponsor's document for a review of the narcolepsy studies.

OASHS

The sponsor performed two controlled trials in patients with OASHS-Study 303 and Study 402

Study 303

This was a randomized, double blind, placebo controlled parallel group study performed at 39 centers in the US. In this trial, patients were randomized to receive either Provigil 200 mg/day (N=104), 400 mg/day (N=101), or placebo (N=104). Patients in this trial were classified as either CPAP compliant (CPAP used for at least 4 hours/night for at least 70% of nights) or CPAP partially compliant (CPAP used < 4 hours/night on >30% of nights). The double blind period lasted for 12 weeks.

The primary outcome measures were the Maintenance of Wakefulness Test (MWT) and the CGI-C. In the MWT, the patient is instructed to stay awake in a darkened room. At each visit, the patient has four 20 minute sessions performed at two hour intervals. The score for that visit is the average of the time it takes for the patient to fall asleep over the 4 sessions (if they do not fall asleep, the time is considered to be 20 minutes).

Secondary outcomes in this study were the Epworth Sleepiness Scale (ESS; a subjective rating scale assessing how easily the patient falls asleep during 8 different situations; as the sponsor notes, a score of 10 or more indicates ES) and the Psychomotor Vigilance Task (PVT; an objective test in which the subject responds to the appearance of a visual stimulus; the primary parameter measured in this test is the number of lapses, defined as brief episodes of

nonreactivity; other measures include the reaction time).

The following chart displays the results of the primary analyses of the Last observation Carried Forward (LOCF) data set for the intent-to-treat (ITT) population :

	200 mg (N=88)	400 mg (N=86)	Pbo (95)	P-value
Change from Baseline MWT (minutes)	1.6	1.5	-1.1	<0.0001
CGI-C	(see Sponsor's Table 15, p. 46)			<0.0001

The results of the analyses of the secondary outcomes are as follows:

	200 mg (N=98)	400 mg (N=92)	Pbo (N=99)	P-value
Change from Baseline ESS	-4.5	-3.7	-1.8	<0.0001
PVT-Change From Baseline	(N=77)	(N=76)	(N=80)	
Median Reaction Time	-20.4	-8.3	1.35	<0.0001
	(N=78)	(N=76)	(N=80)	
Number of Lapses	-2.8	-0.8	-0.2	0.0006

An analysis of the patients who were CPAP partially compliant (N=35) revealed no trends for significance on the MWT, and essentially no trends in favor of drug on the CGI-C.

Study 402

This was a 4 week, randomized, placebo controlled, double blind, parallel group study in which CPAP compliant patients were randomized to receive Provigil 400 mg/day (N=77) or placebo (N=80). The primary outcome in this study was the change from baseline in the ESS; multiple other secondary outcomes were also assessed, including the CGI and MSLT (Multiple Sleep Latency Test, a test similar to the MWT, except that subjects are instructed to not resist falling asleep; it is scored in the same way as the MWT). The following results were seen:

	400 mg (N=75)	Pbo (n=80)	P-value
Change from Baseline ESS	-4.6	-2	<0.0001

CGI-C (See sponsor table 23, page 54) 0.016

	(N=67)	(n=77)	
Change from Baseline MSLT (minutes)	0.99	-0.23	0.02

SWSD

The sponsor performed one controlled trial in patients with SWSD; Study 305.

Study 305

This was a randomized, placebo controlled, double blind, parallel group study in patients with SWSD performed at 28 centers in the US. Two groups of patients were to be enrolled; those who worked 5-10 night shifts/month and those who worked more than 10 night shifts/month, with at least 3 shifts occurring on consecutive days. In this trial, patients took their treatment 30-60 minutes before the start of each night shift and not at other times. The primary outcomes were the MSLT and the CGI-C. The outcomes were assessed in a laboratory setting during the night hours that the patient ordinarily worked. The vast majority of patients in this study (>90%) worked at least 10 night shifts/month.

Secondary measures included the PVT and the Karolinska Sleepiness Scale (KSS; a 9 point scale in which the patient rates him or herself from 1 [very alert] to 9 [very sleepy]), another subjective measure of sleepiness.

In this study, patients were randomized to either Provigil 200 mg/day (N=99) or placebo (N=110). The following chart presents the primary results:

	200 mg (N=86)	Pbo (95)	P-value
Change from Baseline MSLT (minutes)	1.70	0.34	0.002

CGI-C	(N=89) (see Sponsor's Table 29, p. 61)	(N=104)	<0.0001
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The results of the analyses of some secondary outcomes are given below:

	200 mg (N=85)	Pbo (95)	P-value
Change from Baseline KSS	-1.5	-0.4	<0.0001
PVT-Change From Baseline	(N=77)	(N=83)	
Number of Lapses	-4.1	6.1	0.007

COMMENTS

The sponsor has submitted the results of three newly conducted clinical trials, and two previously conducted clinical trials, which they believe provide substantial evidence that Provigil (modafinil) is effective in the treatment of Excessive Sleepiness Associated with Disorders of Sleep and Wakefulness. The sponsor's approach has been to study the effects of the drug on three different diseases, which they believe are representative of three categories of sleep disorders associated with ES, which the sponsor has in turn created and defined by what they presume to be distinct pathophysiologic mechanisms. To summarize, the sponsor has proposed the following pathophysiologic categories, and has studied the "representative" disease indicated:

Pathophysiologic Category	Representative Disease
Sleep-wake dysregulation	Narcolepsy
Sleep Disruption	OSAHS
Circadian Misalignment	SWSD

The sponsor has proposed that a demonstration of effectiveness in these three diseases supports a general claim of effectiveness in the treatment of ES associated with Disorders of Sleep and Wakefulness.

There is considerable precedent for the approval of drugs for a given symptom that appears in multiple clinical contexts. Typically, the requirements for the approval as a general treatment for such a symptom is a showing that the symptom is successfully treated in several of those clinical contexts. A common example would be the approval of a drug to treat “pain”, based on a finding that pain is successfully treated in several “models” (e.g., post-surgical, tension headache, dental pain, etc.). Given such a showing, the Agency has been willing, in certain circumstances, to grant a “global” or general claim for the treatment of the symptom. Based on discussions with the Division, the sponsor proceeded with an attempt to identify representative clinical “models” in which ES occurs; the clinical program described represents their approach to the problem.

However, in order for us to conclude that these data do, in fact, support such a general claim, we must conclude that the clinical “models” chosen here adequately represent the universe of clinical conditions subsumed under the sponsor’s proposed overarching category; that is, Disorders of Sleep and Wakefulness. It is worth noting that the sponsor’s classification of sleep disorders is their own creation, based on their view of the pathophysiology underlying various clinical conditions. It is fair to say that the underlying pathophysiology of sleep disorders is not completely understood, and therefore we would be interested in knowing whether or not you believe that the sponsor’s approach to classifying these diseases is appropriate. Further, even if their grouping of diseases is felt to be appropriate, we need to ask if a demonstration of effectiveness in the three diseases studied reliably permits the inference that Provigil will successfully treat ES in all of the other conditions not studied. For example, does a showing of effectiveness in Narcolepsy allow us to predict that Provigil will be effective in Recurrent Hypersomnia, or does a showing of effectiveness in OSAHS permit us to conclude that Provigil is effective in Restless Leg Syndrome, or does a showing of effectiveness in SWSD permit us to conclude that Provigil is effective in patients with Time Zone Change Syndrome? It will be necessary for us to conclude that this is so before we grant a global claim of the sort proposed by the sponsor (other possibilities exist: it is, of course, possible that one could conclude that the classification scheme is appropriate, but that in only one or two of the categories was the disease studied a valid “model”). If the Committee concludes that the data do not support the sponsor’s proposed, or any other, global claim, do the data support any other (perhaps disease specific) claim?

There is at least one other general question we would like the Committee to discuss.

The sponsor has chosen to assess Provigil’s effect on the objective measures MWT or the MSLT. These measures are widely used in the field, but it is worth asking if the sponsor should have, instead, assessed the drug’s effect with more direct, or perhaps face valid, measures of sleepiness. For example, one could imagine that, instead of the laboratory based MSLT or MWT, one could count

episodes of falling asleep during the day in patients with narcolepsy, or motor vehicle accidents during the day in patients with OSAHS, or number of work-related accidents while patients with SWSD were working. We are very interested to hear the Committee's views on this issue.

We have additional questions related to the specific results in the specific disease studied.

In the OSAHS studies, the changes from baseline between drug and placebo in sleep latencies were quite small; although analyses of the global measures and other secondary measures also yielded statistically significant between-treatment differences, we can fairly ask if the differences seen are clinically meaningful. Further, the vast majority of the patients were CPAP compliant, at least as defined by the study protocol. As a result, we have no useful information about the effects of Provigil in OSAHS patients who are not compliant with CPAP. If the Committee concludes that the drug is effective in patients with OSAHS, is it appropriate to include in the approval patients who are not CPAP compliant? In addition, it is possible that, in these latter patients, a decrease in ES during the day may predispose these patients to remain CPAP non-compliant (that is, in these patients, their primary complaint might be ameliorated); we are interested in the Committee's views on these, and related, issues and questions (such as, if these patients remain CPAP non-compliant, is this an unacceptable outcome).

In the SWSD studies too, the numerical results on the MSLT are small; again, even though analyses of the other outcomes demonstrated statistically significant between-treatment differences in favor of Provigil, we must ask if these results can be considered to document a clinically meaningful benefit in these patients.

Although the sponsor's intention was to enroll mostly patients who worked a night shift only a few nights/month, the study enrolled almost entirely patients who essentially worked the permanent night shift. Although I noted the "representativeness" of the chosen disease to serve as a model for other diseases above as a general issue, it is worth noting it here to be discussed in this context. Specifically, we need to know whether the Committee believes that the results obtained in these "permanent" shift workers can generalize to those with much more intermittent shift work (we are also, of course, still quite interested to know if the Committee also feels that SWSD is a reasonable model for the other so-called disorders of Circadian Mis-alignment).

In addition, patients with SWSD have great difficulty sleeping during the daytime. If Provigil decreases their ES during the night (when they are supposed to be awake), it is fair to ask if this effect has any deleterious effect on the patient's attempts to sleep during the day, and whether the sponsor has adequately assessed this possibility. Indeed, we would be interested in the Committee's views on whether or not the sponsor has adequately evaluated the effects of

Provigil, either in the short or long-term, on appropriate sleep in any of these populations.

Of course, we are interested not only in the Committee's views on the issues raised here, but also in any other issues you feel are pertinent. I look forward to seeing you later this month, and I thank you for your efforts.

Russell Katz, M.D.