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Quick Pulse

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FDA Peripheral and Central Nervous System Drugs Advisory Committee

Meeting on Cephalon's Provigil (modafinil)

Bethesda, Maryland
September 25, 2003

The FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted on Thursday, September 25, 2003, to recommend that Cephalon's Provigil (modafinil) get an expanded label, but not necessarily quite as broad as the company wants.

1. Were the definitions used by Cephalon appropriate? **Yes**
2. Were the three categories of excessive sleepiness appropriate? **Yes**
3. If the drug works in one disorder in a category, will it work in all disorders in that category? **Mixed vote**
4. Was there sufficient evidence for a broad label for excessive sleepiness? **Tie vote**
5. Is Provigil safe for the broad indication. **Yes**
6. Was the claim in obstructive sleep apnea (OSAHS) proven? **Yes, unanimously**
7. Was the claim in Shift Work Sleep Disorder (SWSD) proven? **Yes**

Provigil got orphan-drug status in 1998 to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy, and Cephalon had sought a broad, new label: "…for the treatment of excessive sleepiness associated with disorders of sleep and wakefulness…" The PDUFA date for an FDA decision is October 20, 2003, and it appears that the biggest issue will be the extent of the label, not whether or not Cephalon will get an expanded label.

A Cephalon official noted that approximately 20 million Americans work non-standard schedules. Reportedly, 66% of workers would change their work schedule if they could, and 2%-5% of adults have a sleep-related difficulty associated with working non-standard hours. Almost one in four night workers are thought to meet the minimal diagnostic criteria SWSD.

A sleep expert, speaking on behalf of Cephalon, defined excessive sleepiness (ES) as "a symptom of difficulty in maintaining wakefulness and increased propensity to fall asleep even in inappropriate circumstances and in situations which interfere with activities of daily living." He estimated that 5%-15% of the population experience ES for one of three reasons:

1. Behavioral, environmental and other extrinsic causes, which are the most common reasons.

2. Medical or psychiatric conditions (e.g., Parkinson's, medications, seasonal affective disorders, etc.).
3. Disorders of sleep and wakefulness, which includes narcolepsy.

In support of its application, Cephalon submitted data from five new studies of Provigil. These are summarized in the table on page 2. On safety, the company concluded: "The types and incidences of adverse events are similar to the current Provigil label." The most common adverse events were headache and nausea. An official also showed data on nCPAP usage, concluding, "Our studies show Provigil treatment did not interfere with nCPAP use in patients with residual ES associated with OSAHS."

Provigil doesn't keep people awake at night when it is bedtime because the plasma level is pretty much gone in 12 hours. An FDA official commented, "Presumably, if you took this just before bed, it would not be a good idea."

FDA Concerns

Dr. Russell Katz, Director of the FDA's Division of Neuropharmacologic Drug Products, outlined the key FDA concerns:

Broad claim

The bottom line was that FDA officials are concerned whether the studies conducted can be extrapolated to other sleep conditions. Dr. Katz asked, "What lets us conclude reliably that, in fact, these diseases are interchangeable in a different category? How do I know if Provigil works in shift work that it must work in jet lag?"

Dr. Katz said there is precedent for this type of claim, "Typically, the symptom is studied in several (not all) clinical models in which it occurs and you hope that you can infer that it works against the symptom regardless of the model." Examples include analgesics that may be studied in a couple of pain models to show that the drug works against pain regardless of the setting. The question is whether the agency can extrapolate to settings not studied. The FDA believes it is critical to understand the pathophysiology and etiology of sleep disorders in order to make this extrapolation, and the agency wanted to know if the three areas chosen by Cephalon are appropriate to do that.

- Sleep wake dysregulation – Provigil already is approved in narcolepsy.
- Sleep disruption – Sleep apnea was studied.
- Circadian misalignment – Shift work sleep disorder was studied.

Dr. Robert Temple, Director of the FDA's Office of Medical Policy, Center for Drug Research and Evaluation, and also the Acting Director of Drug Evaluation 1 (which is in charge of oncology, neurology and cardiac drugs) agreed that Cephalon's request has precedent – even when the disease models are in dispute: "I can think of some of the cases where we do seem to treat symptoms with many origins. We ask people to study a few pain models and then get general pain indication. However, not everyone agrees on the best pain models. And it turns out menstrual cramps don't track well with other pain. So, even in most established places where we treat a symptom, it is not perfect. Then, there are cases where we treated a surrogate like blood pressure. We don't ask the origin of the hypertension, but there is a minority in cardiology who think we should."

Dr. Katz kept drawing the discussion back to the generizability of the Provigil findings. He said, "I want to make it explicit how this situation differs, in part, in a fundamental way, from what we typically do. Typically, we approve a drug for a specific symptom or disease, and we are very empirically-driven. If patients are better, we approve the drug. We don't usually have – or never have – a complete understanding of the pathophysiology of the disease or the mechanisms of the drug. We just know the patients are better. We rarely extrapolate beyond the studies. Here, obviously, there is empirical data of efficacy, but we are being asked to extrapolate those results beyond the conditions studied. Typically, when you do that, we have to pretty much believe we understand the pathophysiol-

Provigil Label Expansion Studies

Study	Description	Patients on Drug and Dose	Primary Endpoint: Change from baseline (drug vs. pbo)	MSLT: Change from baseline (drug vs. pbo)
Narcolepsy 301	9-week, double-blind, randomized, placebo-controlled, parallel group	95 at 200 mg; 86 at 400 mg	200 and 400 mg: MWT: +2.3 vs. -0.7 (p<.001)	1.9 vs. 0.5 (p<.01)
Narcolepsy 302	9-week, double-blind, randomized, placebo-controlled, parallel group	83 at 200 mg; 86 at 400 mg	200 mg: MWT: +2.2 vs. -0.7 (p<.001) 400 mg: 2.0 vs. -0.7 (p<.001)	2.0 vs. 1.3 (p=.2)
OSAHS 303	12-week, double-blind, randomized, placebo-controlled, parallel group, CPAP compliant	110 at 200 mg; 108 at 400 mg	200 mg: MWT: +1.6 vs. –1.1 (p<.001) 400 mg: MWT: +1.5 vs. –1.1 (p<.001)	N/A
OSAHS 402	4 week, randomized, double-blind, placebo-controlled	77 at 400 mg	ESS: 4.6 vs. 20 (p<.001)	1.0 vs. -.03 (p=.02)
SWSD 305	12-week, double-blind, randomized, placebo-controlled, parallel group	99 at 200 mg	N/A	MWT: 1.7 vs. 0.3 (p<.01)

ogy of the disease and the mechanisms of action of the drug, so we can predict with a high level of certainty that the drug will work in disorders/diseases where it was not studied. So this is unusual. It is not that it can't be done, and it has been done in the past, but this is a fundamentally different approach."

Cephalon officials and experts cited studies, laboratory experiments, workshops, etc., insisting the constructs have been "systematically validated." One expert said, "All of these disorders decrease cortical activation in the hypothalmus…and if you give modafinil, you wind up with greater activation of cortical activity."

Does Provigil work for jet lag? A sleep expert said it does, explaining, "We did studies on how rapidly the drug affects performance, and the effect is very rapid, certainly within an hour, and by 2 hours it is at a therapeutic level and sustains for its half life of about 12 hours."

Was it appropriate to extrapolate the findings to all shift workers including rotating shift workers? Generally, the panel did not have a problem applying the SWDS findings to other shift workers.

Clinical value

Provigil showed statistically significant improvement over placebo in sleep apnea studies, but the changes were numerically small. The FDA wanted to know if the panel thought the differences were clinically significant.

Dr. Temple commented, "Total sleep is the same…so this doesn't help a shift worker go to sleep…If I hypothesized that this helps you stay away -- not unlike coffee, but probably better – then that may be the best basis of your argument."

The FDA wanted to know if the panel was concerned with treating symptoms without knowing the cause, and that did bother several panel members. The chairperson said, "What is a concern to me is treating a symptom without knowing the cause. In this case, it seems to me we have a potentially large issue, and the underlying disease might be exacerbated by relieving this symptom." Another panel member said, "It will be hard for clinicians to know when to prescribe (Provigil)...They will be presented with sleepy patients, and it will be difficult for them to know when to prescribe it."

A Cephalon expert disagreed, saying, "The first step is to educate physicians on the diagnosis and treatment of sleep disorders…(But) there is an analogy to insomnia…This is the flip side of that…and we know more about what generates sleepiness than insomnia." A panel member responded, "Using this you may have a greater chance of missing the underlying cause (of the sleepiness)…This approval opens the door considerably…Many insomnia patients will complain of being sleepy in the daytime, and I wonder if, fairly quickly, they may be given symptomatic treatment with Provigil without adequate evaluation, and whether they might have apnea. We see many insomnia patients who turn out to have bad apnea. I would worry about someone too quickly being given a stimulant to treat insomnia that is due to apnea."

CPAP compliance

There was some concern by the committee that Provigil use would interfere with compliance with CPAP use. If Provigil is effective, the FDA wants to know if the use of Provigil could encourage patients to become -- or remain -- CPAP non-compliant and the long-term consequences, if any, of that.

A Cephalon official said, "We want to say, if patients are not optimally managed with CPAP therapy, then they shouldn't use Provigil, but even in CPAP compliant patients, some individuals get refractory symptoms." A panel member said, "One wonders if there should be a suggestion in the label that patients on chronic therapy need to be evaluated in a sleep lab."

Appropriateness of the pivotal trial endpoints of MWT and MSLT and the effect size shown

The expert consultants on the panel agreed the endpoints were appropriate, and the effect size generally was considered sufficient to have clinical implications. One panel member worried, "I wonder if we would be giving (shift workers) a false sense of security (with this drug)." A Cephalon expert said, "SWSD patients are sleepier even than narcoleptic patients…They are a vulnerable subset…on average they have a lapse (in attention) every two minutes…and these are people doing everything from driving to operating car plants...That could have important safety implications."

The difference in magnitude of change in MWT in the various studies did not appear to be an issue. The panel seemed to accept the change as clinically relevant and sufficient.

PUBLIC WITNESSES

A representative of the National Sleep Foundation urged the panel and the FDA to put greater emphasis "on the root causes of sleepiness, so it can be treated." He called sleepiness a significant public health issues and compared it to controlling a contagious disease. He commented, "You can lose your driver's license for narcolepsy, but not for shift working."

The executive director of the American Sleep Apnea Association (ASA) emphasized, "It may be easier to take Provigil, but it doesn't make CPAP unnecessary. This must be made clear in advertising and labeling. Sleepiness does carry risks, but modafinil must not be seen as a panacea…The ASA is clearly committed to seeing that, should it be approved, that it be prescribed appropriately…We think

Cephalon needs to educate physicians on the appropriate role (for Provigil)."

VOTES AND SELECTED PANEL COMMENTS

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?
Positive Vote: 7 yes, 1 abstain

The sponsor believes that the above group can be divided into three categories, based on the presume cause of the excessive sleepiness. The categories are: sleep-wake deregulations, sleep disruption, and circadian misalignment. Does the Committee agree with this classification?
Positive Vote: 7 yes, 1 abstain

Does the Committee Agree that the disorders studies by the sponsor – narcolepsy, obstructive sleep apnea (OSAHS), and shift work sleep disorder (SWSD) – are representative of the three categories described above? If the drug works in one disorder, does that mean it will work in all disorders in that category?
Negative Vote: 5 no, 3 yes
A panel member said, "In any one of the three conditions tested, the patients are representative. Not every patient got a response…I also understand from the data presented that the company is not making a claim that Provigil is treating any specific underlying disease, just an amelioration of symptoms which is common to a broad variety of diseases that would be specified. I felt the data was such that, in fact, there are three conditions, each one representative of an example of that class. If I thought they were treating disease, I would say no, but they are treating symptoms, so I have to say yes." The panel chair disagreed, arguing that Provigil is treating pathophysiology not symptoms, "I don't think there is a common pathophysiology…I feel strongly the sponsor made a wise choice in what to study – the most common disorder in each category – (but) here they are grouping very diverse conditions in each of three categories…and the pathophysiology of each is likely to differ so substantially that I'm concerned about the effects in the different conditions."

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…"?
Mixed Vote: 4 yes, 4 no
Even the sleep experts on the panel were divided on this issue. A panel member said, "To me (efficacy) is synonymous with approval…I still think that there is not enough information to make a broad application for a variety of diagnoses." Another panel member said, "How can we say it is effective for that population when the treated subjects still have an MSLT of 3.8 – these are people we would be worried about driving even with medication, despite clear clinical improvement." However, Dr. Katz commented, "The treatments, in general, that we approve are not cures." The chairperson concluded: "I think the company proved the three indications, but not the general statement."

Has the sponsor demonstrated that Provigil can be used safely for this broad indication?
Positive Vote: 6 yes, 2 no

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?
Positive Vote: unanimous with 8 yes

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?
Positive Vote: 6 yes, 2 no

CEPHALON REACTION

Cephalon officials said they expect an approvable letter by the PDUFA data, and final approval by the end of 2003. The company is consolidating its existing ~330 person sales force, part of which handles Provigil and another part of which sells its pain medication, Actiq. In addition, Cephalon plans to add another ~120 sales reps starting in 4Q03 to be ready for a launch in February or March 2004. There will be an emphasis on reaching general practitioners.

An official said, "I think the results today are a positive…The vote on safety was the first time that has happened on Provigil. Certainly safety will not be the concern going forward." Another official said, "(The votes) should give people safety reassurance if they had previously been concerned."

If the company doesn't get the broad label it is seeking, it still plans an aggressive launch. An official said, "Clearly, the indication may vary, but the target audience is the same – sleep specialists, pain, neurologists, and GPs who are big, big users of pain meds like Actiq and will be big users of Provigil as well." Another official said, "It really doesn't matter what the label is as long as (we can sell it)."

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