DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Frank Baldino, Jr., Ph.D.
Chairman and Chief Executive Officer
Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355 USA

RE: NDA # 20-717
Provigil® (modafinil) Tablets [C-IV]
MACMIS # 14707

WARNING LETTER

Dear Dr. Baldino:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a promotional piece distributed on behalf of your company to the Maryland Department of Health and Mental Hygiene's Pharmacy and Therapeutics Committee (Committee) on August 17, 2006. This piece recommends or suggests uses for Provigil (modafinil) Tablets [C-IV] (Provigil) that have not been approved by FDA, and thus creates new "intended uses" for Provigil for which the product lacks adequate directions, broadens the indication for Provigil, and fails to communicate any risks associated with its use. Therefore, the piece misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) & (f)(1); 321(n), and FDA implementing regulations. 21 C.F.R. §§ 201.5(a); 201.128; *cf.* 21 C.F.R. § 202.1(e)(6)(i). Furthermore, the FDA-approved product labeling (PI) for Provigil did not accompany the promotional piece, in violation of 21 C.F.R. § 201.100(d). Finally, Cephalon failed to submit the piece to FDA under cover of Form FDA-2253, as required by 21 C.F.R. § 314.81(b)(3)(i). These violations present serious public health and safety concerns.

Background

The Indications and Usage section of the PI for Provigil states:

> PROVIGIL is indicated to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder [SWSD].
>
> In OSAHS [Obstructive Sleep Apnea/Hypopnea Syndrome], PROVIGIL is indicated as an adjunct to standard treatment(s) for the underlying obstruction. If continuous positive airway pressure (CPAP) is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating PROVIGIL. If PROVIGIL is used adjunctively

with CPAP, the encouragement of and periodic assessment of CPAP compliance is necessary.

In all cases, careful attention to the diagnosis and treatment of the underlying sleep disorder(s) is of utmost importance. Prescribers should be aware that some patients may have more than one sleep disorder contributing to their excessive sleepiness.

Use of Provigil is also associated with numerous risks. For example, the PI includes the following important safety information:

WARNINGS

Patients with abnormal levels of sleepiness who take PROVIGIL should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking PROVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

PRECAUTIONS

General

...Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.

* * *

Broadening of Indication/Lack of Adequate Directions for Use

On August 17, 2006, Dr. Harry Kerasidis, M.D. delivered a presentation on Provigil to the Committee at a public meeting. Dr. Kerasidis specifically stated that he was at the meeting "to speak on behalf of Cephalon for modafinil, for inclusion on the Preferred Drug List."[1] As part of his presentation, Dr. Kerasidis provided the Committee with a handout entitled "The Utility of Provigil (modafinil) in the Medical and Psychiatric Population." This promotional piece is false or misleading because it states or suggests that Provigil is safe and effective for use in the treatment of various disorders associated with fatigue, sleepiness, or inattentiveness, when in fact, Provigil is not indicated for fatigue at all and is indicated only for specific groups of patients with excessive sleepiness, as stated above (see Background section).

The second page of the piece states:

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[1] *Public Meeting of the State of Maryland Department of Health and Mental Hygiene Preferred Drug List Pharmacy and Therapeutics Committee,* August 17, 2006 (statement of Dr. Harry Kerasidis).

Provigil (modafinil) has utility in the treatment of...some cases of insomnia....Provigil (modafinil) also has utility in the treatment of other neurologic and psychiatric disorders associated with fatigue, sleepiness, or inattentivness [sic]:

Multiple Sclerosis Related Fatigue

- MS affects 300,000 Americans. 10-20% of these individuals suffer from chronic fatigue. Provigil (modafinil) is very effective in relieving the fatigue related to MS....

Parkinson's Disease Related Fatigue

- Parkinson's and the medications used to treat Parkinson's Disease often results in daytime sleepiness, which often can be offset with the use of Provigil (modafinil).

Chronic Fatigue Syndrome [sic] Fibromyalgia, & chronic pain conditions

- The fatigue related to CFS [chronic fatigue syndrome] and Fibromyalgia often responds to Provigil (modafinil). Many of the medications used to treat these conditions also lead to impairing daytime sleepiness which often can be offset by Provigil (modafinil).

Attention Deficit Disorder

- Double blind placebo controlled studies have shown significant improvements in multiple cognitive measures in this population without the risks attendant to the traditional stimulants used to treat this condition [referring to attention-deficit hyperactivity disorder].

Depression

- In a retrospective case series, modafinil was found to augment actions of antidepressants, especially in patients with residual tiredness or fatigue....

Provigil is not indicated for insomnia or fatigue, which refers to a loss of desire or ability to perform, an outcome that was not directly examined in the clinical studies supporting Provigil's approval. Provigil also is not indicated for the treatment of any of the neurologic or psychiatric disorders cited above. Indeed, the promotion of Provigil for the treatment of ——————————is particularly troubling given that shortly before the Committee meeting, Cephalon received a "not approvable" letter dated ——————from FDA with respect to a supplemental new drug application seeking approval for the use of modafinil for the treatment of this disease.

In addition, the promotional piece suggests that Provigil can improve some of the consequences of a condition referred to in the piece as Sleep Disorder Related Fatigue (SDRF). Specifically, on the first page of the handout, the following claims are presented:

- "Corporate America is losing $18 billion each year to lost productivity due to Sleep Disorder Fatigue."
- "Nearly 1/3 of all fatal-to-the-driver heavy trucking accidents are due to driver fatigue. For every driver lost, an average of 4 innocent by-standers are also lost."
- "Approximately 25% of night/rotating shift workers meet criteria for **SWSD** resulting in increased risks of motor vehicle accidents, work related accidents and errors, and clinically significant impairment in social and occupational function." (emphasis original)

We acknowledge that the claims in these bullets may be true and that people who suffer from diagnosed sleep disorders such as SWSD may also suffer from fatigue and that SDRF may negatively impact both the economy (due to lost productivity) and society (due to increased accidents). However, your presentation of these claims in this promotional piece for Provigil misleadingly implies that Provigil is proven to be effective in treating SDRF when, as stated above, Provigil is not indicated for the treatment of fatigue, which would include SDRF. Furthermore, while Provigil is indicated to improve wakefulness in patients with excessive sleepiness associated with SWSD, the second and third bullets imply that Provigil can be beneficial with respect to avoiding driving-related accidents or improving social and occupational function associated with SWSD. The first precaution in the PI specifically provides, however, that due to its effect on the central nervous system, Provigil "may alter judgment, thinking or motor skills." Thus, while Provigil may improve wakefulness, it does not necessarily follow that Provigil is beneficial with respect to either avoiding driving-related accidents or improving social and occupational function associated with SWSD. Indeed the PI specifically cautions patients about "operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities."

The promotional piece also suggests that Provigil can be used to treat patients with excessive sleepiness resulting from sleep disorders other than narcolepsy, OSAHS, and SWSD by stating that "Provigil (modafinil) has utility in the treatment of other sleep disorders that cause excessive daytime sleepiness including idiopathic hypersomnolence syndrome, delayed sleep phase syndrome...." Provigil has not been demonstrated to be safe and effective in treating the full spectrum of recognized subclasses of sleep disorders associated with excessive sleepiness. Indeed, a generalized indication [redacted] was denied for Provigil by FDA in a letter dated October 20, 2003, and Provigil instead was granted specific indications for excessive sleepiness associated with OSAHS and SWSD.

Finally, the piece broadens the indication for Provigil by omitting an important limitation to Provigil's indication with respect to OSAHS. The piece states that Provigil is FDA approved for "**Persistent hypersomnolence in treated obstructive sleep**

apnea."(emphasis original) However, the piece fails to indicate that Provigil is approved as an adjunct to continuous positive airway pressure (CPAP) treatment, and that a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating Provigil (see Background section).

Omission of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The handout fails to include any risk information, including a critical caveat from labeling, which is that "Patients with excessive sleepiness, including those taking PROVIGIL, should be frequently reassessed for their degree of sleepiness and, if appropriate, **advised to avoid driving**...."(emphasis added). This is especially concerning given the claims implying that Provigil is beneficial with respect to avoiding driving-related accidents, as discussed above.

Failure to Provide Adequate Directions for Use

The PI was not disseminated with the promotional piece, in violation of 21 CFR 201.100(d)(1).

Failure to Submit

FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. You did not submit a copy of the promotional piece referred to in this letter to FDA under cover of Form FDA-2253, as required by 21 C.F.R. § 314.81(b)(3)(i).

Conclusion and Requested Actions

For the reasons discussed above, the promotional piece misbrands Provigil in violation of the Act, 21 U.S.C. §§ 352(a) & (f)(1); 321(n), and FDA implementing regulations. 21 C.F.R. §§ 201.5(a); 201.128; *cf.* 21 C.F.R. § 202.1(e)(6)(i). Furthermore, the PI for Provigil did not accompany the piece, as required by 21 C.F.R. § 201.100(d). Finally, Cephalon failed to submit the piece to FDA under cover of Form FDA-2253, as required by 21 C.F.R. § 314.81(b)(3)(i).

DDMAC requests that Cephalon immediately cease the dissemination of violative promotional materials for Provigil such as those described above. Please submit a written response to this letter on or before March 12, 2007, stating whether you intend to comply with this request, listing all violative promotional materials for Provigil that are the same as, or similar to, those described above, describing how you conducted your search for similar pieces, and explaining your plan for discontinuing use of such materials. Because the

violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 14707 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Provigil comply with each applicable requirement of the Act and FDA implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Abrams
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