CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-875

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-875

Cephalon, Inc.
Attention: Paul M. Kirsch
Senior Director, Regulatory Affairs
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Dear Mr. Kirsch:

Please refer to your New Drug Application (NDA) dated March 31, 2005, received March 31, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nuvigil™ (armodafinil) Tablets 50 mg, 100 mg, 150 mg, and 250 mg.

We acknowledge receipt of your additional submissions dated:

May 1, 2006	December 19, 2006	February 23, 2007	March 20, 2007
June 30, 2006	February 7, 2007	February 27, 2007	
November 13, 2006	February 13, 2007	March 16, 2007	

The June 30, 2006 submission constituted a complete response to our April 28, 2006 action letter. In addition, your December 19, 2006 submission, which was a major amendment submitted within three months of the previous user fee goal date of December 31, 2006, extended the user fee goal date to March 31, 2007.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the issues described below.

CLINICAL

Our review of data pertaining to modafinil and armodafinil and the risk for serious skin and other hypersensitivity reactions is complete. Based on the rate of serious skin and other hypersensitivity reactions with modafinil in clinical trials and the post-marketing setting, we are requesting that you adopt a bolded statement in the Warnings section describing this risk. We are also requesting that you add a Warning statement describing the risk of angioedema with armodafinil.

Of particular concern to us is the rate of skin reactions resulting in drug discontinuation (and often treatment) in pediatric clinical trials of modafinil. Including the one case of possible Stevens Johnson

Syndrome (subject 062338, the 7-year-old patient we have discussed at length, and about which we have additional comments; see below), there were a total of 8 (8/1622; 0.5%) skin reactions leading to study discontinuation in modafinil-treated children and adolescents,[1] and no cases in placebo-treated children or adolescents.

Regarding the one 7-year-old boy with a severe rash, we acknowledge your view that this patient did not have Stevens Johnson Syndrome (SJS), but atypical Erythema Multiforme Major (aEMM). Based on our review of this case, we cannot entirely rule out the possibility that this was, in fact, a case of SJS. Regardless of the specific diagnosis, however, we are convinced by the particulars of this case that this was a serious, drug-induced rash (indeed, by your own admission, aEMM can be drug-induced, and can be fatal). For these reasons, we believe that this case supports the conclusion that modafinil can cause serious rash, with potentially devastating consequences.

Although there were no cases of serious skin reactions in modafinil or armodafinil clinical trials in adults, the post-marketing reporting rate of serious skins reactions in adults treated with modafinil is above the background rate, which supports a causal role for modafinil. Using a conservative case definition, we calculated a reporting rate of Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) of about 6 cases/million person-years for patients of all ages (although we acknowledge that all of the reported cases occurred in adults), based on four cases[2] reported to the FDA Adverse Event Reporting System (AERS) and about 704,000 total patients-years of exposure (about 2 million unique individuals) in the United States. This rate is above the accepted background rate of about 1-2 cases/million patient-years of exposure, even without accounting for expected under-reporting of cases. In addition to these cases of SJS/TEN, there were eight cases of possible multi-organ hypersensitivity reactions, including a case of Drug Rash with Eosinophilia and Systemic Symptoms in a 15 year old (DRESS; case US 017698).

Although the data you present indicate that no definite or probable cases of SJS were identified in the European studies, we do not find these data reassuring, particularly regarding the possibility that the risk for modafinil-associated serious skin reactions may be higher in children than in adults. While the European registry data you present is of excellent quality, the estimated exposure to modafinil in these databases (15,500 patients in EuroSCAR, 31,446 in RegiSCAR and 11,700 patients in German SCAR, a small minority of whom are estimated to have been children) is too small to allow for the adequate estimate of drug-associated risk for an adverse event with a rate on the order of that which we believe to be associated with modafinil use. In addition, case ascertainment may have been incomplete. In EuroSCAR, population coverage varied widely among countries, and only community cases were captured (i.e., cases of SJS/TEN with onset during hospitalization for another illness would not have been captured).

We anticipate that we will ask you to adopt a similar bolded Warning for modafinil (Provigil).

In addition to the bolded Warning describing the risk for serious skin reactions, we ask that you add a statement in the Warnings section describing the two apparent type I hypersensitivity reactions that were observed in armodafinil-treated patients in clinical trials (subject 0441026 developed urticaria and angioedema; subject 1884236 developed a "hypersensitivity reaction, dysphagia, and bronchospasm"). The rate of angioedema in the armodafinil database of 0.13% (1/724 in armodafinil-

[1] Cases 020001, 062338, 18004, 056180, 315, 18001, 13011, and 24004
[2] Cases US019026, US016653, US016856, and US016624.

treated patients vs. 0/471 placebo-treated patients) is close to the rate observed with the Angiotensin Converting Enzyme inhibitors.

To better characterize the risk for serious skin and other hypersensitivity reactions in patients of all ages treated with modafinil and armodafinil, we recommend that you improve the follow-up of such cases in ongoing and future clinical trials of modafinil and armodafinil, as well as in the postmarketing setting. Any ongoing or future studies with modafinil and armodafinil should incorporate into the protocol a rigorous and standardized approach to the assessment and follow-up of these cases, including evaluation by a dermatologist, laboratory assessments (including complete blood counts and liver function tests), photographs, biopsy results, and if applicable, final diagnosis, treatment received, and information regarding clinical outcome.

Please propose additional strategies to minimize the potential for this risk. Elements of such a strategy might include an educational component (including statements that armodafinil is not approved for use in pediatric patients), and frequent (e.g., quarterly) reports of any severe rash and other hypersensitivity reactions. This plan would apply to Provigil as well.

LABELING

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Nuvigil upon approval of this application. The base document used for our draft labeling is your labeling submitted on June 30, 2006. Depending upon your response, labeling may need to be amended further.

To facilitate review of your resubmission, please provide a highlighted or marked-up copy that shows all changes and identify which version of Nuvigil labeling was used as the base document. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

NON-CLINICAL

We acknowledge your response regarding the assessment of the carcinogenic potential of modafinil. However, the information in your response has been previously considered and no new data were submitted to address this deficiency. Therefore, either a 2-year study or an appropriate alternative assay assessing the carcinogenic potential of armodafinil still needs to be conducted. As a reminder, the carcinogenicity studies may be conducted post-marketing. In addition, a timeline should be proposed for study conduct and submission of a final study report for each study.

CLINICAL PHARMACOLOGY

You have communicated that the evaluation of the drug-drug interaction potential between armodafinil and substrates of P-glycoprotein has been completed. As communicated in our April 28, 2006 action letter, this evaluation may be submitted as a post-marketing commitment. Alternatively, these evaluations may be submitted as a part of your response to this letter. Submission of these evaluations will not affect the review period for a future action date, if a complete response is submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

PROMOTIONAL MATERIALS

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

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

OTHER

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Tamy Kim, PharmD, Regulatory Project Manager, at (301) 796-1125.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
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NDA 21-875

Cephalon, Inc.
Attention: Paul M. Kirsch
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Dear Mr. Kirsch:

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We acknowledge receipt of your additional submissions dated:

June 7, 2005	August 12, 2005	October 28, 2005	January 25, 2006	April 5, 2006
June 10, 2005	August 19, 2005	October 31, 2005	January 27, 2006	
June 13, 2005	September 27, 2005	December 16, 2005	February 10, 2006	
June 24, 2005	September 29, 2005	January 12, 2006	March 24, 2006	

We also acknowledge receipt of your submission dated April 6, 2006, which contained an integrated report of urinalysis data. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

This New Drug Application provides for the use of Nuvigil™ (armodafinil) Tablets [the R-enantiomer of Provigil (modafinil) Tablets] to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, narcolepsy and shift work sleep disorder.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, you must address the following issues.

CLINICAL

1. As you know, the Agency is currently evaluating the materials you have recently submitted to your NDA for modafinil in connection with the single possible case of Stevens Johnson Syndrome (SJS) in a pediatric patient. If our review confirms that this is a case of SJS, a prominent statement describing this event will need to be placed in product labeling for Nuvigil, despite the fact that Nuvigil will not be approved for use in the pediatric population. Final labeling, therefore, cannot be approved until our evaluation of that case, and the larger issue of modafinil's capacity to cause serious rash, is complete.

In an attempt to further characterize the potential for Nuvigil to cause serious rash, we ask you to re-examine your controlled and uncontrolled clinical trial database for modafinil for all possible cases of serious rash. In particular, you should search your entire clinical trials database using all appropriate search terms to identify any possible such cases, followed by a critical examination of all potential cases identified. We would be happy to discuss with you an appropriate search strategy. We also ask you to provide us with all narratives (discontinuations and serious drug reactions) from the clinical trial database, dating back to the original NDA approval that contain any reference to skin adverse event.

2. We have recently received a MedWatch report (Manufacturer #US016978), dated March 29, 2006, of a 31 year old man who died secondary to cardiac failure potentially resulting from multi-organ hypersensitivity syndrome related to modafinil treatment. We are in the process of further evaluating this case; as part of this evaluation, please submit any additional information on this case, including confirmation that the patient had been receiving Trileptal for many years prior to the onset of the event and information on when Provigil was discontinued. In addition, we request that you examine your modafinil database, both clinical trials and post-marketing experience, for cases of multiorgan hypersensitivity. Again, we would be happy to discuss with you an appropriate search strategy for identifying and evaluating any possible cases that you identify.

NON-CLINICAL

A full battery of nonclinical studies was not conducted or requested to support an NDA for armodafinil based on the presumption that the studies conducted for armodafinil would demonstrate similarity to modafinil and the belief that the nonclinical studies of modafinil were adequate. We believe that you have demonstrated that armodafinil and modafinil are pharmacologically and toxicologically similar; however, we have concerns regarding the adequacy of certain aspects of nonclinical data for modafinil. Based on the available information, it would appear that effects on pre- and postnatal development and carcinogenic potential have not been adequately assessed.

You submitted two pre- and post-natal studies of modafinil. In Study DS-93-017, modafinil was administered to rats at doses up to 100 mg/kg/day from gestation day 15 through postpartum day 21. That study was inadequate due to the lack of any maternal toxicity and insufficient duration of dosing. In Study DS-95-022, modafinil was administered at higher doses (up to 200 mg/kg/day) from gestation day 7 through postpartum day 20. Although Study DS-95-022 was otherwise adequate, it does not appear that neurobehavioral parameters were assessed. b(4)

b(5)

Regarding the assessment of carcinogenic potential, you have conducted a 78-week dietary study in mouse, a 104-week dietary study in rat, and a 26-week dermal study in the Tg.AC transgenic mouse with modafinil. The Tg.AC mouse assay was conducted to fulfill a Phase 4 requirement for modafinil due to the inadequacy of the 78-week dietary study. We acknowledge that you received concurrence on the use of this model from both the Agency and the Carcinogenicity Assessment Committee; however, the dermal Tg.AC is not currently considered appropriate for evaluation of an oral drug, based on the potential inability of the dermal model to adequately assess the carcinogenic potential of metabolites (formed following oral administration) or in a full battery of tissues (i.e., the Tg.AC strain is genetically 'initiated' for skin carcinogenicity; cf. Leder A et al. *Proc Natl Acad Sci USA* 87:9178-

9182, 1990; Holden HE et al. *J Appl Toxicol* 18(1):19-24, 1998). Considering the intended patient population, we consider it critical that the assessment of carcinogenic potential of armodafinil be adequate. Therefore, either a 2-year study or an appropriate alternative assay on armodafinil needs to be conducted.

[redacted] the carcinogenicity studies may be conducted post-marketing; a time line should be proposed for study conduct and submission of a final study report for each study. If you believe that you have additional information that would justify the adequacy of the available nonclinical data regarding these two issues, please submit them for review. b(4)

PROPRIETARY NAME

As discussed in our telephone conversation dated April 13, 2006, we have determined that the use of your proposed proprietary name, Nuvigil, is acceptable. However, this determination is a tentative decision because it is Agency policy to re-evaluate proposed proprietary names approximately 90 days prior to the expected final approval of the application.

We are still concerned that there may be confusion between Nuvigil and Norinyl (any strength). As we agreed in the April 13, 2006 telephone conversation, you will submit any reports of actual or potential medication errors involving these two drugs as 15-day safety reports. This requirement will also apply to reports that you receive in which the similarity of the two names is noted by an interested party (for example, a report to you from a pharmacist in which the similarity of the names is noted), even if no dispensing error has occurred.

Additionally, we remind you of your agreement to include language in your promotional materials describing the potential for this medication error.

CLINICAL PHARMACOLOGY

1. We note that a tighter dissolution specification for Nuvigil was conveyed to you in our December 27, 2005 communication, and that you agreed, in your January 25, 2006 submission, to the revised specification. Accordingly, the agreed upon dissolution method and specifications for NUVIGIL tablets are as follows:

   Apparatus: USP apparatus 2 (Paddle)
   Stirring Speed: 50 rpm
   Dissolution Medium: 0.1N HCl
   Volume of Medium: 900 mL
   Temperature: 37.0 °C
   Specification: Q = [redacted] in 30 minutes

2. We ask that you provide information pertaining to the drug-drug interaction potential between armodafinil and substrates (e.g., digoxin) of P-glycoprotein through literature or an in vitro study as a post-marketing commitment. This evaluation should address whether armodafinil is a substrate or inhibitor (or inducer) of P-glycoprotein. b(4)

LABELING

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Nuvigil upon approval of this application. The base document used for our draft labeling is the draft labeling contained in your March 31, 2005 submission. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been revised. Please also note that we have embedded in the text of the attached draft labeling several "Notes to Sponsor" requesting additional clarification. Depending upon your response and results from the additional analyses requested in this letter, labeling may need to be amended further.

To facilitate review of your resubmission, please provide a highlighted or marked-up copy that shows all changes and identify which version of Nuvigil labeling was used as the base document.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

SAFETY UPDATE

When you respond to the above deficiencies, please include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

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Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

37 Page(s) Withheld

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/s/

Russell Katz
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