CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020717

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-717

Cephalon, Inc.
Attention: Paul Nemeth, Ph.D.
145 Brandywine Parkway
West Chester, PA 19380-4245

Dear Dr. Nemeth:

Please refer to your new drug application dated December 27, 1996, received December 30, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Provigil® (modafinil) Tablets.

We acknowledge receipt of your additional correspondences and amendments dated:

February 14, 1997
March 27, 1997
March 31, 1997
April 8, 1997
April 9, 1997
April 10, 1997
April 11, 1997
April 18, 1997
May 1, 1997
May 2, 1997
May 5, 1997
May 12, 1997
June 2, 1997
June 3, 1997
June 12, 1997
June 16, 1997
June 17, 1997
June 23, 1997
July 3, 1997
July 8, 1997
July 17, 1997
July 28, 1997
July 30, 1997
July 31, 1997
August 18, 1997
September 2, 1997
September 5, 1997
September 9, 1997
September 15, 1997
September 19, 1997
September 22, 1997
September 26, 1997
October 7, 1997
October 9, 1997
October 20, 1997
November 5, 1997
November 11, 1997
November 14, 1997

The User Fee goal date for this application is December 30, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests or comments.

Labeling Issues

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Provigil® Tablets upon its approval. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been extensively revised and/or expanded to include new subsections. Please note that we

have embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label.

1. Dosage and Administration Section

The data from the two effectiveness trials do not demonstrate any consistent, increased benefit of 400 mg/day compared to 200 mg/day. Further, you have not submitted sufficiently detailed data regarding the long term exposure to 400 mg/day given as a single daily dose to permit a statement in labeling about the long term safety of this dose. For these reasons, we have concluded that 200 mg/day, given as a single dose, is the recommended dose.

If you submit the additional data requested below, and our review supports it, you may include a statement in labeling that describes the tolerability of a single 400 mg daily dose in long term use, but you will still not be able to state explicitily or imply that it is known to confer additional benefit beyond that associated with a 200 mg single daily dose.

Safety Issues

1. You state that you cannot be certain that the numbers of patients in the dose/duration cells in your tables of the foreign data represent separate discrete individuals, raising the question of the accuracy of your statements that 2305 subjects have been exposed to Modafinil.

Before we can approve your application, we must have a complete, accurate accounting of all subjects/patients exposed to Modafinil, with accurate corresponding dose/duration data for this cohort. Your re-submission should address this issue clearly and completely. Our staff will be happy to discuss with you the way in which this data should be submitted.

2. Please clearly present accurate duration (and corresponding safety experience) data for subjects who have received single daily doses of 400 mg or greater; this information is currently unobtainable from your submission. In addition, please present duration and corresponding safety data separately for subjects who have received daily doses of 400 mg or greater as twice a day dosing; there may be some overlap in these 2 cohorts (single daily dose and twice a day dosing).

3. Please submit laboratory data for the foreign studies. Describe in detail how often laboratory measurements were assessed in the various foreign cohorts.

4. Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Pharmacology

[redacted]

2. Your reproductive toxicology package is inadequate for evaluation of the full spectrum of potential effects of Provigil on fertility or on the fetus. With the exception of a peri- and post-natal study, which was conducted in 1995, the reproductive toxicology studies were not conducted in compliance with Good Laboratory Practices (GLP) regulations and their value for predicting potentil toxicity is marginal. In addition, the fertility and teratology studies were carried out at doses which were too low to obtain appropriate exposures (ICH Guideline for Industry "Detection of Toxicity to Reproduction for Medicinal Products", page A-4, Selection of Dosages). The high dose used in the rat teratology study was associated with some minimal fetal toxicity, and the potential magnitude of fetal effects should be better characterized given that the patient population for which Provigil is indicated includes women of child-bearing potential.

[redacted]

Biopharmaceutics

1. Please submit for our review information regarding the interconversion of enantiomers.

2. The drug-drug interaction study design between clomipramine and modafinil was inadequate because the dose of clomipramine was too low and the study only examined single doses. We recommend that a more appropriate study be designed and conducted on the interaction between modafinil and clomipramine (or imipramine) on subjects including those who are deficient of CYP2D6.

3. Please submit for our review information on modafinil interactions with CYP3A and CYP2C19 enzyme substrates (especially narrow therapeutic drugs as CYP2C19 substrates).

4. We ask that the following final dissolution methodology and specification be adopted for Provigil® Tablets (100mg and 200mg):

[redacted]

Chemistry, Manufacturing, and Controls

1. [redacted]

Scheduling

A final decision regarding the appropriate schedule into which Provigil® Tablets will be classified has not been made.

Promotional Material

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

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

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

If you have any questions, please contact Melina Malandrucco, R.Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely yours,

/S/

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

NDA: 20-717
Trade Name: Provigil
Generic Name: modafinil
Applicant Name: Cephalon
Division: HFD-120
Project Manager: Melina Malandrucco, R.Ph.
Approval Date:

PART I

IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a. Is it an original NDA? — Yes

   b. Is it an effectiveness supplement? — No
   If yes, what type? (SE1, SE2, etc.)

   c. Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") — Yes

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study. — N/A

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data: — N/A

   d. Did the applicant request exclusivity? — Yes

   If the answer "yes," how many years of exclusivity did the applicant request? — 5 yrs/ 7 yrs (orphan)

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? No

   If yes, what is NDA number

   If yes, what is Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? No

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

APPEARS THIS WAY ON ORIGINAL

PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

No

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

1) If yes, explain:

2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

If yes, explain:

If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Investigation #2, Study #:

Investigation #3, Study #:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

   a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

      Investigation #1

      Investigation #2

      Investigation #3

      If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

      NDA: Study:

      NDA: Study:

      NDA: Study:

   b. For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

      Investigation #1

      Investigation #2

      Investigation #3

      If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

      NDA: Study:

      NDA: Study:

NDA: Study:

c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #: Study #:

Investigation #: Study #:

Investigation #: Study #:

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND#: Explain:

Investigation #2
IND#: Explain:

Investigation #2
IND#: Explain:

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
Explain:

Investigation #2
Explain:

Investigation #3
Explain:

Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

If yes, explain:

/S/

Melina Malandrucco, R.Ph.
Project Manager
DNDP, HFD-120

Paul Leber, M.D.
Director
DNDP, HFD-120

cc:
Original NDA
Division File
HFD-120/ Malandrucco
HFD-85/Holovac

APPEARS THIS WAY ON ORIGINAL

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-717 Trade (generic) names Provigil (modafinil)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 and #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach

copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

___ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

APPEARS THIS WAY ON ORIGINAL

/S/ [redacted]

Signature of Preparer

12-2-97

Date

APPEARS THIS WAY ON ORIGINAL

cc:
Orig NDA
HFD-120 Division File
NDA Action Package

Date: November 26, 1997

Telecon with Paul Nemeth, PhD, Senior Director, Regulatory Affairs. 145 Brandywine Parkway, West Chester, PA 19380-4245

Reference: Scheduling and Abuse of Modafinil NDA #20-717
Tel: (610) 344-0200

Dr. Nemeth returned my earlier voice message call.

I opened the discussion by informing Dr. Nemeth that the Jasinski data made the drug look a lot like methylphenidate. Also, the drug self-administration data in primates was pretty compelling implying significant abuse and potential dependence producing properties. I asked how Cephalon would respond to a CIII recommendation, and told the sponsor that the similarity in study results of modafinil to methylphenidate and cocaine has led us to even consider CII as an option.

Cephalon opposes CIII, and "if could see into crystal ball, they would request no scheduling." Per Nemeth, there are no reports of abuse. [redacted] this is well known, yet it has [redacted] as yet as far as they know. It is difficult to inject the drug or smoke it. The difference is because the type of substance abuse females differs from males; females abuse more Rx products.

The drug substance comes from [redacted] and will be imported into the U.S. Dosage forms will be manufactured in [redacted] There are no current plans for manufacturing the drug in US, that is, not until they look for "a big indication" specifically ADHD.

Next year, they are planning ADHD studies. Long developing plan will have to show the effect on growth & development. Long term data is needed. A first study will involve 80 pediatric patients at doses of 100 mg start & go up & down 50 mg. Indication is tied to school year, because the diagnosis often comes from the school system.

Nemeth will call back at 1PM, with Contreras (preclin) & Civil (clin). Nemeth said that a decision to request CIII could be made by this group since they are small enough of a company.

1 PM Call Back:

Later in the day the sponsor called back. Two more consultants (Jasinski & Cicero) were on the line. It was the Jasinski clinical abuse liability study - 14 volumes in total - that was submitted just prior to the deadline (two days prior) under PDUFA

without getting an extension for review as a major clinical amendment. The data came in to the FDA with a request for CIV. The drug showed significant gender differences in "drug liking", as "amphetamine-like", euphoria scale with an early peak effect. Responses over the next few hours increased significantly on the LSD scale. Jasinski maintained that modafinil was no more abuseable than phentermine (which is water soluble as opposed to modafinil). He would provide a demonstration of such; anorectic abuse he maintained is not likely and possible off-label use (for ADHD and staying awake for performance enhancement) is "not abuse, but misuse."

Jasinsik wanted to know what the driving force was for wanting the drug controlled more strictly. I responded that it was the similar pharmacology of modafinil to methyphenidate & cocaine in abuse liability studies, and fairness not just to this sponsor but to the sponsors of the comparator drugs that the drugs on the marketplace be regulated similarly if they are pharmacologically similar.

Jasinski said that he would FEDEX me data to show that modafinil is comparable to phentermine which is in CIV. Unfortunately, such a direct comparison of modafinil to phentermine was not studied.

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee

Attention: Dan Boring, Chair (HFD-530)
9210 Corporate Blvd, Room N461

Thru: Paul Leber, M.D. /ISI/ for Paul Leber 7/23/97
Director, DNDP
(HFD-120)

From: Division of Neuropharmacologic Drug Products (HFD-120)
Attention: Melina Malandrucco, R.Ph
(Project Manager) (301) 594-5526

Date: July 23, 1997

Subject: Request for re-evaluation of a Trademark for Proposed New Drug Product
(Review from August 1996 enclosed)

Proposed Trademark: PROVIGIL (modafinil tablets) NDA:20-717

Indication: Narcolepsy

Note: A response is requested as soon as possible. Thank you.

cc.
Original NDA 20-717
HFD-120/Division Files
HFD-120/Katz/Rappaport /ISI/ 7/23/97
HFD-120/Blum/Heimann

Consult #630 (HFD-120)

PROVIGIL no established name

A review revealed several names which sound like or look like the proposed name: Proventil, Provera. The Committee does not believe there is a significant potential for confusion involving these names with the proposed name.

A discussion was held on whether or not the proposed name was fanciful as defined in 21 CFR 201.10(c)(3). The Committee notes that the indication for this product is for the treatment of narcolepsy, and that the name could imply " for wakefulness" (PRO = for, VIGIL = wakefulness). However, the Committee does not believe that the proposed name is misleading or fanciful in this respect.

The Committee has no reason to find the proposed name unacceptable at this time but reserves their recommendation until after a USAN is selected and the proposed non-proprietary name is submitted to the Committee for reconsideration. Furthermore, the Committee notes the proposed name has been submitted for review very early in the review process (IND stage). Under such circumstances, the Committee routinely recommends the proposed name be re-evaluated once an NDA has been submitted and the application is closer to approval since the universe of potential sound-alike/look-alike proprietary names is constantly changing.

/S/ [redacted] 8/1/96, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY ON ORIGINAL