DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-717

Cephalon, Inc.
Attention: Paul M. Kirsch
Senior Director, Regulatory Affairs
145 Brandywine Parkway
West Chester, PA 19380

Dear Mr. Kirsch:

Reference is made to your Proposed Pediatric Study Request submitted on June 5, 2003, for Provigil (modafinil) Tablets to IND 42,873.

To obtain needed pediatric information on modafinil, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies in pediatric and adolescent patients with excessive sleepiness resulting from obstructive sleep apnea (OSA) and narcolepsy.

We are asking for information from three types of studies:

Study Type I: Pharmacokinetic/Tolerability Study

Study Type II: Efficacy and Safety Study

Study Type III: One Year Safety Study

TYPE I STUDIES: PHARMACOKINETIC AND TOLERABILITY STUDIES

You must obtain pharmacokinetic data to provide information pertinent to dosing of the study drug in the relevant pediatric population. Therefore, you should perform preliminary tolerability studies (in which kinetic data can be obtained) to fully explore the range of tolerated doses, before conducting the definitive efficacy and safety studies. Adequate pharmacokinetic and tolerability data from studies in a single indication would be sufficient to meet this requirement.

Patient Age Groups

Patients must be $\geq$ 6 and < 17 years old.

Study Design

In the required PK/tolerability studies, appropriate PK parameters such as T_{max}, $t_{1/2}$, C_{max}, AUC_{0-t}, K_e (elimination rate constant), apparent V_d (volume of distribution), and apparent oral clearance, as defined by fraction of bioavailable oral dose F, i.e., Cl/F must be calculated.

Patients for PK evaluation must be representative of the larger study population with respect to age and gender. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available at [http://www.fda.gov/cder/guidance/1970dft.pdf].

The PK data in the tolerability study should come from traditional multiple dose PK studies that explore the range of tolerated doses. If blood sampling is a limiting factor in the younger subject's, population analysis using a combination of frequent and sparse sampling from different studies (including the efficacy studies) may be performed for these age groups. If a sparse sampling approach is used, approximately 3-4 blood samples per patient in 3-4 time brackets covering the full concentration-time profile after the modafinil dose must be collected. Blood samples in population studies must not be collected at fixed time points. You should be aware that a guidance document on population pharmacokinetic studies is available under [www.fda.gov/cder/guidance/1852fnl.pdf].

Number of Patients to be Studied or Power of the Study to be Achieved

Sufficient numbers of subjects must be studied to adequately characterize the pharmacokinetics and tolerability of modafinil within the specified age ranges. For the PK/tolerability study this would include at least 12 children per dose, with equal distribution across the age ranges ($\geq$ 6 to < 12 and $\geq$12 to <17). A larger number would be needed to perform sparse sampling than for traditional PK studies. A relatively uniform distribution of patients throughout the age range must be studied.

Drug Information

Dosage form(s): Age appropriate modafinil formulations of known bioavailability must be used. If different formulations are used in the clinical trials, the relative bioavailability between the formulations must be assessed (the use of bioavailability data generated in adults is acceptable).

Route of administration: Oral

If children in the lower age ranges have not been evaluated, consider dosing for these studies on a mg/kg basis extrapolated from the adult dose, with a goal of establishing a comparable exposure (C_{max} and AUC) as in adults.

Study Endpoints

Plasma concentrations of modafinil, modafinil acid, and modafinil sulfone must be determined. Pharmacokinetic parameters such as C_{max}, t_{max}, AUC, t½, apparent clearance (CL/F), and apparent volume of distribution (V/F) and other metrics as appropriate must be calculated for each analyte.

Potential effects of covariates such as dose, age, body-weight, body-surface area, and renal function may be included in the analysis, and used in the dosing recommendations if deemed appropriate. The potential influence of other covariates, such as race, gender, or formulation, on pharmacokinetic metrics must also be investigated. The influence of concomitant medications should be considered.

Statistical Information

Statistical information must include descriptive statistics of modafinil pharmacokinetic parameters. These results must be compared to pharmacokinetic metrics obtained in adults (the use of adult historical control data is acceptable).

TYPE II STYDIES: EFFICACY AND SAFETY STUDIES

Safety and Efficacy Studies are required for each of the two indications. These are summarized below.

Obstructive Sleep Apnea (OSA)

Type of Study

A single multi-center pediatric double-blind, placebo controlled, randomized, parallel group efficacy and safety study in patients with excessive daytime sleepiness resulting from obstructive sleep apnea (OSA). The study must be at least 6 weeks in duration.

Indication to be Studied (i.e., objective of each study)

To determine efficacy and short term safety in patients with excessive daytime sleepiness from OSA despite adequate treatment that includes both surgical intervention (where indicated) and continuous positive airway pressure (CPAP).

Study Design

Randomized, double-blind, placebo-controlled, parallel group, efficacy and short-term safety outpatient study. The trial must maximize the opportunity to detect a treatment effect of the drug, if there is one in this population. Specifically, if you perform a flexible dose ranging study or a fixed dose study that does not fully explore the range of tolerable doses in this population and that study fails to detect an effect of the drug, this will not be considered to have met the requirements of this request. Therefore, we strongly recommend that the trial be a fixed dose study that includes fixed doses that fully explore the tolerated dose range in this population. A randomized withdrawal design would be acceptable so long as patients at entry had been treated for at least 6 weeks and several doses including placebo are studied.

Age Groups to be Studied

Patients must be $\geq$ 6 to <17 years old.

Number of Patients to be Studied or Power of the Study to be Achieved

The study must have a sufficient number of patients to provide at least an 80% power to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in the adult trials that were the basis for this drug's approval in adults. This number must also be sufficient to adequately characterize short-term safety. There must be an approximately equal distribution across the age ranges ($\geq$ 6 to < 12 and >12 to <17). The studies must also define an interpretable dose-response relationship, including the identification of a no-effect dose.

Entry Criteria (i.e., inclusion/exclusion criteria)

Only patients >6 and $\leq$ 16 years old with OSA who exhibit excessive sleepiness despite receiving adequate treatment for the underlying airway obstruction (to include CPAP and surgery where appropriate) must be enrolled in the trial. The diagnosis of OSA must be confirmed with polysomnography.

Study Endpoints

As in the adult studies, two co-primary outcomes must be used. One must be a subjective global measure, e.g., the Clinical Global Impression. The second must be a direct objective measure of sleepiness, e.g., multiple sleep latency test (MSLT). All measures must be justified as to their applicability to the pediatric population.

Drug Information

Use an age appropriate formulation of known bioavailability in the studies described above. A formulation you develop for use in children must meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency.

Statistical Information, Including Statistical Assessments

This trial must have a detailed statistical plan. The trial must be designed with at least 80% statistical power for each of the co-primary endpoints to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in adult trials for sleep apnea, at conventional levels (alpha=0.05, 2-tailed) of statistical significance. Both co-primary endpoints must show a statistically significant difference to conclude efficacy.

<u>Narcolepsy</u>

Type of Study

A single multi-center pediatric double-blind, placebo controlled, randomized, parallel group efficacy and safety study in patients with excessive sleepiness resulting from narcolepsy. The study must be at least 6 weeks in duration.

Indication to be Studied (i.e., objective of each study)

To determine efficacy and short term safety in patients with excessive daytime sleepiness from narcolepsy.

Study Design

Randomized, double-blind, placebo-controlled, parallel group, efficacy and short-term safety outpatient study. The trial must maximize the opportunity to detect a treatment effect of the drug, if there is one in this population. Specifically, if you perform a flexible dose ranging study or a fixed dose study that does not fully explore the range of tolerable doses in this population and that study fails to detect an effect of the drug, this will not be considered to have met the requirements of this request. Therefore, we strongly recommend that the trial be a fixed dose study that includes fixed doses that fully explore the tolerated dose range in this population. A randomized withdrawal design would be acceptable so long as patients at entry had been treated for at least 6 weeks and several doses including placebo are studied.

Age Groups to be Studied

Patients must be $\geq$ 6 to <17 years old.

Number of Patients to be Studied or Power of the Study to be Achieved

The study must have a sufficient number of patients to provide at least an 80% power to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in the adult trials that were the basis for this drug's approval in adults. This number must also be sufficient to adequately characterize short-term safety. There must be an approximately equal distribution across the age ranges ($\geq$ 6 to < 12 and >12 to <17). The studies must also define an interpretable dose-response relationship, including the identification of a no-effect dose.

Entry Criteria (i.e., inclusion/exclusion criteria)

Only patients >6 and $\leq$ 16 years old with narcolepsy confirmed through a formal evaluation in a sleep laboratory must be enrolled.

Clinical Endpoints

As in the adult studies two co-primary outcomes must be used. One must be a subjective global measure, e.g., the Clinical Global Impression. The second must be a direct objective measure of sleepiness, e.g., multiple sleep latency test (MSLT). All measures must be justified as to their applicability to the pediatric population.

Drug Information

Use an age appropriate formulation of known bioavailability in the studies described above. A formulation you develop for use in children should meet standards for marketing approval. If you cannot develop a potentially marketable formulation, you will need to document the attempt to do so, and the Agency will consider another formulation that is standardized and palatable. Full study reports of any relative bioavailability studies should be submitted to the Agency.

Statistical Information, Including Statistical Assessments

This trial must have a detailed statistical plan. The trial must be designed with at least 80% statistical power for each of the co-primary endpoints to show a difference between drug and placebo equivalent to the median drug-placebo difference seen in adult trials for narcolepsy, at conventional levels (alpha=0.05, 2-tailed) of statistical significance. Both co-primary endpoints must show a statistically significant difference to conclude efficacy.

TYPE III STUDIES: SAFETY

Safety data must be collected in all of the controlled efficacy trials for the above indications. Routine safety assessments must be collected at baseline and appropriate follow-up times, i.e., vital signs, weight, height (using a stadiometer), routine clinical laboratory measures (to include urinalysis, electrolytes, glucose, renal and liver function tests, CBC), ECGs, and monitoring for adverse events.

Specific safety concerns in short and long-term studies include cognitive and behavioral (anxiety, nervousness and symptoms of mania and psychosis) effects of the drug. Monitoring must include interviews by a child psychologist or psychiatrist and a standardized test of behavior (e.g., the Achenbach Child Behavior Checklist). Changes in cognition associated with both short and long term use of modafinil must also be determined. Age-appropriate cognitive assessments must also be performed. Other adverse events that are of specific interest include effects on growth, potential bone marrow suppression, and hypertensive effect of modafinil. Blood pressure must be carefully monitored throughout all studies.

We have specific concerns related to the occurrence of leukopenia with the use of modafinil in the pediatric and adolescent subjects. Accordingly, we are requesting that at least one hundred (100) patients, $\geq$ 6 to <17 years of age, treated with differing therapeutic doses of modafinil be followed for one year with monthly manual blood counts and differentials.

The longer-term safety studies may be open label, e.g., a longer-term open label extension from the controlled efficacy trials and/or separate longer-term open label safety studies, or from controlled studies, e.g., a longer-term safety and efficacy trial. Adequate longer-term safety data must be distributed amongst the different indications studied. Because we view the two patient populations as fundamentally different we ask that you collect information separately for the following groups. For each grouping (by age and indication) listed below, the minimum number of patients indicated besides that grouping must be exposed to study drug for 6 months. The

long-term safety data must be at or above the dose or doses identified as effective (for that age and indication) in an adequately designed trial, as described above. If an adequately designed and conducted effectiveness trial fails to detect a drug effect, you must still collect long-term safety data, at doses at least as high as the doses currently used in treating patients off-label with this drug.

OSA, ages 6-12 years	at least 50 patients
OSA, ages 12-16 years	at least 50 patients
Narcolepsy, ages 6-12 years	at least 50 patients
Narcolepsy, ages 12-16 years	at least 50 patients

LABELING THAT MAY RESULT FROM THIS STUDY

Appropriate sections of the label may be changed to incorporate the findings of the studies.

FORMAT OF REPORTS TO BE SUBMITTED

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES

Reports of the above studies must be submitted to the Agency on or before **December 2008**. Please keep in mind that pediatric exclusivity attaches only to existing patient protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

RESPONSE TO WRITTEN REQUEST

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request, you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written

agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted **as a supplement to NDA 20-717** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the Federal Register a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Richardae C. Taylor, Pharm.D., Regulatory Health Project Manager, at 301-594-5793.

Sincerely,
{See appended electronic signature page}

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

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

/s/

Robert Temple
6/17/04 07:34:12 PM