DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21875/S-023

SUPPLEMENT APPROVAL

Cephalon, Inc.
Attention: Adam Uchimoto
Associate, Regulatory Affairs
41 Moores Road
Box 4011
Frazer, PA 19355

Dear Mr. Uchimoto:

Please refer to your Supplemental New Drug Application (sNDA) dated July 28, 2016, received July 28, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nuvigil® (armodafinil) tablets.

This Prior Approval supplemental new drug application provides for the addition of information regarding serious dermatologic reactions and Drug Reaction with Eosinophilia and System Symptoms (DRESS)/Multiorgan Hypersensitivity to the Warnings and Precautions section (5.1 and 5.2), revisions to Section 5.5 (Psychiatric Symptoms), the addition of a new Adverse Reactions; Postmarketing Experience subsection (6.2), revisions to comply with the Pregnancy and Lactation Labeling Rule (PLLR), and revisions to the Drug Abuse and Dependence section (9), including the addition of a new subsection, Dependence (9.3).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Nuvigil was approved on June 15, 2007, we have become aware of a signal for growth restriction following in utero exposure. A signal for forms of pre- or postnatal abnormal growth restriction following in utero exposure, including microcephaly, small for gestational age, and failure to thrive, was identified in the ongoing Nuvigil and Provigil Pregnancy Registry and reported in the Registry Year 6 status report submitted to the Provigil NDA (20717) on July 28, 2016. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of pre- or postnatal growth restriction following in utero exposure.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3167-1 Maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the maternal, fetal, and infant

outcomes of women exposed to modafinil or armodafinil during pregnancy to outcomes in an unexposed control population in the Metropolitan Atlanta Congenital Defects Program (MACDP). Collect and classify major structural and functional birth defects identified in the perinatal period through 12 months of life. Outcomes should include microcephaly, small for gestational age, low birth weight, and intrauterine growth restriction. Information on other medication use and on maternal breastmilk feeding practices should also be included.

The timetable you agreed to on February 6, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission Date:	April 2017
Interim Annual Report	July 2018
Interim Annual Report	July 2019
Interim Annual Report	July 2020
Interim Annual Report	July 2021
Interim Annual Report	July 2022
Interim Annual Report	July 2023
Interim Annual Report	July 2024
Interim Annual Report	July 2025
Interim Annual Report	July 2026
Study Completion Date:	January 2027
Final Study Report Submission Date:	July 2027

Submit the protocol to your IND 068517, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o)

on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Vandna Kishore, Regulatory Project Manager, at Vandna.Kishore@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Alice Hughes, MD
Deputy Director for Safety
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

ALICE HUGHES
02/07/2017