



NDA 021947/S-009

SUPPLEMENT APPROVAL

Cephalon, Inc
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Susan Franks, M.S.
Director, Regulatory Affairs

Dear Ms. Franks:

Please refer to your Supplemental New Drug Application (sNDA) dated April 2, 2009, received April 3, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FENTORA (fentanyl buccal tablets).

We acknowledge receipt of your amendments dated April 13, May 1, July 22, September 11, November 17, and December 17, 2009, and February 22, May 13, June 11 and 30, July 28, August 6, and November 23, 2010, and February 2, and July 1, 7, and 12, 2011.

This "Prior Approval" supplemental new drug application provides for a proposed risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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, 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 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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON LABELS

We acknowledge your July 7, 2011, submission containing final printed carton labels.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS, if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. The details for the REMS requirements and the need for a single, shared system to implement the REMS for all members of the Transmucosal Immediate-Release Fentanyl (TIRF) Products were outlined in our REMS notification letter dated November 12, 2010.

Since FENTORA (fentanyl buccal tablets) was approved on September 25, 2006, we became aware of reports of deaths, including in patients treated for migraine headache and chronic low back pain. In addition, there are increasing numbers of non-opioid tolerant patients being prescribed Fentora, and there have been documented pharmacy-initiated substitutions of Fentora for Actiq, direct switches by physicians from Actiq on a mcg for mcg basis, and incorrect dosing instructions written. The RiskMAP, approved when Fentora was approved, has failed to meet its stated objectives, particularly to ensure proper patient selection (i.e., patients who must be opioid-tolerant), and it has failed to provide adequate education of physicians and pharmacists as evidenced by medication errors with improper dose titration, dosing regimens, conversion of doses from Actiq, and improper product substitution for Actiq. We consider this information to be “new safety information” as defined in section 505-1(b) of FDCA.

Pursuant to 505-1(f)(1), we have also determined that FENTORA (fentanyl buccal tablets) can remain on the market only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of overdose, abuse, addiction, and serious complications due to medication errors that are listed in the labeling. The elements to assure safe use will provide for the education of prescribers and patients so that they are aware of the risks associated with the use of FENTORA and about important information regarding how to use the product safely to help prevent the serious adverse effects noted above. The elements will also assure proper patient selection and dispensing of FENTORA (fentanyl buccal tablets).

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on July 12, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include, but is not limited to, the following:

1. For the assessment of enrollment and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers/distributors, the following data will be tabulated:
 - a. The total numbers and geographic distribution of prescribers enrolled in the FENTORA REMS program, number of new prescribers enrolled during the current reporting period, and number of prescribers who were inactivated
 - b. The total numbers and geographic distribution of pharmacies enrolled in the FENTORA REMS program, number of new pharmacies enrolled during the current reporting period, and number of pharmacies that were inactivated (reported by type of pharmacy, inpatient or outpatient)
 - c. The total numbers and geographic distribution of patients enrolled in the FENTORA REMS program, new patients enrolled during the current reporting period, and number of patients who were inactivated
 - d. The number of completed *Knowledge Assessments* for prescribers and authorized pharmacists, and a tabulation of the number of attempts required to successfully complete the *Knowledge Assessment*
 - e. The total number of wholesalers/distributors enrolled in the FENTORA REMS program, number of new wholesalers/distributors enrolled during the current reporting period, and number of wholesalers/distributors that were inactivated
 - f. A report on the number of pharmacies that returned product because they did not enroll within six months of REMS program launch
2. Dispensing activity for enrolled pharmacies (outpatient); including authorization to dispense data from enrolled outpatient pharmacies
3. For the assessment of program infrastructure and performance:
 - a. A summary and root cause analysis of all unintended system interruptions (e.g., due to system failure, program failure, inaccurate training), including, but not limited to:
 - 1) Barriers or delays in patient access due to:

- a) False negatives: e.g., all entities are enrolled, but system generated a prescription rejection notice
 - b) Prescriber delay in submitting the completed *Patient-Prescriber Agreements* to the FENTORA REMS Program
 - c) Inadvertent enrollment deactivations, or failures to notify enrollees of forthcoming enrollment expirations
 - d) Prescriber who is not aware of FENTORA REMS program (i.e., not enrolled) prescribes FENTORA
 - e) Geographic barriers: lack of enrolled prescribers and/or pharmacies in a patient's local area
 - f) A report on the length of the delay (i.e., how long it took for patient to receive FENTORA after the original prescription was denied by the pharmacy)
- 2) Inappropriate patient access:
- a) False positives: e.g., one or all entities were not enrolled but system verified dispensing/generated a unique authorization code
 - b) Inpatient pharmacy dispensing for outpatient use
- b. An assessment of the process for pharmacies to upgrade their pharmacy management systems, including a report on the time required for outpatient pharmacies to upgrade their pharmacy management systems (mean, maximum and minimum amount of time), and on the number of pharmacies that tried and were unable to modify their systems
 - c. An evaluation of the enrollment process for prescribers, pharmacists, and wholesalers/distributors, including a summary of the method used to enroll (e.g., online, fax), and a report on the quality of the data received (e.g., number of incomplete forms received)
 - d. Report of reasons for and the number of times a "back-up" system was used to validate a prescription, either due to problems at the pharmacy-level, with the Switch or with the FENTORA REMS database
 - e. Call center report, including a summary of frequently asked questions and problems reported, and any needed program enhancements
 - f. A description of the corrective actions taken based on the programs/system tracking of these occurrences
4. Results of surveys conducted of prescribers' and pharmacists' (inpatient and outpatient) understanding and knowledge of the safe use and appropriate prescribing of FENTORA, as described in the FENTORA REMS educational materials and package insert

5. Results of surveys conducted of patients' understanding and knowledge of the serious risks and safe use of FENTORA.
6. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
7. A report on the number of Dear Healthcare Professional letters mailed (prescriber and pharmacy), when the letters were mailed, what information was included in the mailings, and number of returned mailings
8. Results of any prescriber, pharmacy, wholesaler/distributor, and vendor audits conducted, and corrective actions taken during the reporting period
9. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
10. Results of surveillance and monitoring activities for abuse, misuse, and overdose including:
 - a. Signals that indicate misuse, abuse, overdose, or addiction (including patients obtaining prescriptions from multiple prescribers)
 - b. Signals that indicate serious adverse events or deaths related to inappropriate prescribing of FENTORA, such as prescriptions to non-opioid tolerant patients, and prescriptions for inappropriate doses
11. Drug Utilization Data including the following information:
 - a. The number of cumulative initial and continuing prescriptions to date and new initial prescriptions during the reporting period, as well as minimum, maximum, mean and median number of prescriptions per patient
 - b. FENTORA Month-to-Date Sales (Distribution) Report (by type of pharmacy, inpatient or outpatient)
 - c. Data from flagged prescriptions from more than two prescribers to the same patient
 - d. An analysis to evaluate FENTORA REMS utilization patterns including use in non-opioid tolerant patients
12. An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
13. Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including

whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021947 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 021947
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021947
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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, please contact Kimberly Compton, Senior Regulatory Health Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton Labeling
REMS

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

/s/

BOB A RAPPAPORT
07/20/2011