

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022410Orig1s000

OTHER ACTION LETTERS



NDA 022410

COMPLETE RESPONSE

Reckitt Benckiser Pharmaceuticals Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Attention: John D. Pitts, R.Ph., Ph.D.
Manager, Regulatory Affairs

Dear Dr. Pitts:

Please refer to your New Drug Application (NDA) submitted October 20, 2008, received October 21, 2008, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Suboxone (buprenorphine and naloxone) sublingual film.

We acknowledge receipt of your amendments dated October 22 and 30, December 1, 3, 8, and 11, 2008, and January 8, February 4 (2), March 3, 20, 25, and 26, April 6, 20, 28, and 30, June 9, July 24, and August 7 and 14, 2009.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Suboxone sublingual film to ensure that the benefits of the drug outweigh the risks of (1) exposure to Suboxone sublingual film in persons for whom it was not prescribed, including accidental exposure in children and (2) risks of abuse and misuse. The REMS, once approved, will create enforceable obligations.

Your proposed REMS, included in your submission dated October 20, 2008, is not sufficient to ensure that the benefits of Suboxone sublingual film outweigh the risks associated with use of Suboxone sublingual film.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Suboxone sublingual film poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Suboxone sublingual film. FDA has determined that Suboxone sublingual film is a product for which patient labeling could help prevent serious adverse events and that Suboxone sublingual film is a product that has serious risks (relative to benefits) of which patients should be made aware as information concerning the risks could affect patients' decisions to use, or continue to use Suboxone sublingual film. Under 21 CFR Part 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Suboxone sublingual film.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that the Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including, at least, assurance that each patient using the drug is subject to certain clinical monitoring under section 505-1(f)(3)(E) of the FDCA to ensure that 1) each patient is receiving the psychosocial support necessary for safe and effective use buprenorphine, 2) each patient adheres to the conditions of safe use explained to him/her, and 3) each patient is using Suboxone sublingual film appropriately and making adequate progress towards treatment goals.

Timetable for Submission of Assessment: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than every six months for the first 1 year and annually thereafter after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Suboxone sublingual film. Additionally, all relevant proposed REMS materials including any educational materials or forms should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application

can be approved, we will include these documents as an attachment to the approval letter that includes the REMS.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

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

1. A survey of healthcare providers' understanding of the serious risks of Suboxone sublingual film and the need for appropriate patient monitoring and psychosocial support services.
2. A report on the status of the monitoring of patients by healthcare professionals.
3. An evaluation of the effectiveness of the REMS program through an analysis and summary of surveillance and monitoring activities for abuse and misuse and any intervention taken resulting from signals of abuse and misuse. This surveillance and monitoring should include substance abuse treatment programs, private practitioners, ethnographers, and media surveillance.
4. A report on the frequency and consequences of accidental pediatric exposures to Suboxone sublingual film.
5. An evaluation of patients' understanding of the serious risks of Suboxone sublingual film.
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 failures to adhere to distribution and dispensing requirements for the Medication Guide, and corrective actions taken to address noncompliance.
8. Specification of proposed measures that could be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022410
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022410
PROPOSED REMS-AMENDMENT**

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

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

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 nonclinical and clinical studies/trials 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:
 - a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - b. Present tabulations of the new safety data combined with the original NDA data.
 - c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - d. 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 updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

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

Enclosure: REMS Template
 REMS Supporting Document

Appendix A: REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

- A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;
- C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);
- D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;
- E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or
- F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B), (C), and (D), listed above.

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Appendix B: Supporting Document

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
 - a. Additional Potential Elements
 - i. Medication Guide
 - ii. Patient Package Insert
 - iii. Communication Plan
 - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
 - c. Implementation System
 - d. Timetable for Submission of Assessments of the REMS
5. REMS Assessment Plan
6. Other Relevant Information

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
08/21/2009