

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022410Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

INTERIM REMS REVIEW COMMENTS

Drug Name: SUBOXONE Sublingual Film (buprenorphine HCL and naloxone)	BLA/NDA: #22-410	Date: 8/6/10
(b) (4)		Comment Set # 1
DRISK Scientific Leads: Jeanne Perla, Ph.D., Risk Management Analyst Megan Moncur, Risk Management Analyst		Reviewers: DRISK Gita Toyserkani, Pharm.D., Acting Team Leader Marcia Britt, Ph.D., Health Education Reviewer Brian Gordon, MA., Social Science Reviewer DDMAC Mathilda Fienkeng, Pharm.D., Regulatory Review Officer OC Agnes Plante, BSN, RN, Consumer Safety Officer
RCM #: 2010-970		

MATERIALS REVIEWED:

- General Advise Letter to applicant dated March 29, 2010
- SUBOXONE Sublingual Film NDA 22-410
 The following proposed REMS materials received April 30, 2010, were reviewed:
 1. Proposed REMS
 2. Proposed REMS Supporting Document
 3. REMS Instruction Letter to Prescribers
 4. REMS Introductory Letter to Pharmacists
 5. Appropriate Use Checklist
 6. Physician Brochure, “Important Information for Physicians- Frequently Asked Questions”
 7. Pharmacist Brochure, “Important Information for Pharmacists-Frequently Asked Questions”

(b) (4)

INTRODUCTION:

This interim REMS review is to provide preliminary comments on the proposed REMS submitted on April 23, 2010 for SUBOXONE sublingual film (NDA 22-410),

(b) (4)

On October 8, 2002 SUBUTEX and SUBOXONE sublingual tablets were approved for the treatment of opioid dependence with a Risk Management Plan. On October 20, 2008, Reckitt Benckiser submitted a REMS for NDA 22-410. The proposed indication for SUBOXONE sublingual film is for the maintenance treatment of opioid dependence.

(b) (4)

On August 21, 2009, Reckitt Benckiser received a Complete Response Letter for NDA 22-410 stating the proposed REMS was not sufficient to ensure the benefits outweighed the risk. In the CR letter the sponsor was notified that each patient using the drug be subject to certain clinical monitoring under section 5050(f)(3)(E) of the FDCA to ensure

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that 1) each patient is receiving the psychosocial support necessary for safe use and effective use of (b) (4) SUBOXONE, 2) each patient adheres to the conditions of safe use explained to him/her, and 3) each patient is using (b) (4) SUBOXONE appropriately and making adequate progress towards treatment goals.

The sponsor requested a meeting and submitted questions in the meeting background package on October 5, 2009 to discuss their proposed REMS submitted on (b) (4) November 24, 2009, (NDA 22410). Based on the review of the proposed REMS, the Agency provided responses in a General Advice letter to the questions and provided additional comments on the proposed REMS documents.

In the General Advice letter the sponsor was notified that based on the Agencies understanding of the risks of buprenorphine, it was determined that the REMS must include a Medication Guide, elements to assure safe use under 505-1(f)(3)(D) and 505-1(f)(3)(E), an implementation system, and a timetable for the submission of assessments of the REMS. A communication plan was not required as an element of the REMS.

Furthermore, because the risks of buprenorphine for the treatment of opioid dependence are the same, the sponsor was informed that the REMS for the three applications can be the same; however, the Medication Guide may be product specific and not all three products have to share the same Medication Guide. Additionally, the sponsor was informed that the goals of the REMS should be changed to the following: 1) to mitigate the risk of accidental overdose, misuse and abuse and 2) to inform patients of the serious risks associated with the use of SUBOXONE sublingual film (b) (4)

The comments below are OSE/OC/DDMAC's preliminary review of the amended proposed REMS submitted by Reckitt Benckiser on April 23, 2010, which incorporates the goals and the elements as recommended in the General Advice letter of March 29, 2010.

COMMENTS FOR THE SPONSOR

The following comments are on the proposed REMS, appended material and Supporting Document submitted for NDA 22-410. (b) (4)

Please incorporate the changes for all three applications and submit all revised materials within 2 weeks.

1. General Comments

- a. Comments are provided based on the draft Product Labeling (PI). Revise all REMS materials to be consistent with the final agreed upon PI.
- b. Ensure the approved name of each drug is consistent with the PI in all of the REMS material.
- c. Replace (b) (4) with *Reckitt Benckiser* throughout REMS and REMS Supporting Document.

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- d. Once the REMS and appended material are agreed upon, submit a final REMS with all appended materials and the REMS Supporting Document for each application.
- e. Provide a track changes and clean version of all revised materials and documents.
- f. All REMS documents should be dated and paginated to facilitate reviewer document control.
- g. Remove the word (b) (4) from the final documents.
- h. Please submit your revised proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. If certain documents are only in PDF format, they may be submitted as such, but any revisions will need to be identified (e.g. using the PDF Comment & Markup Tool).

2. REMS Goals and Objectives:

The goals of the REMS have been reviewed and found to be acceptable. The separate section titled (b) (4) has been removed from the REMS document but may remain in the Supporting Document.

3. Medication Guide:

- a. Detailed information on the (b) (4) dispensing of the Medication Guide has been deleted from your REMS document, and should be included in your Supporting Document.
- b. The Medication Guide for NDA 22-410 submitted on July 14, 2010 was reviewed and found to be acceptable.

(b) (4)

4. Elements to Assure Safe Use (ETASU):

- a. Revisions were made to the following documents. See appended redline and clean versions:
 - i. **Appendix A (Appendix B – clean version)** for revisions to the proposed REMS document. Please incorporate the changes. The REMS document may continue to undergo revisions by the Agency as the REMS goes through the internal clearance process.
 - ii. **Attachment C (Appendix D – clean Copy)** for revisions to the REMS Instruction Letter to Prescribers
 - iii. **Attachment E (Appendix F – clean Copy)** for revisions to the REMS Introductory Letter to Pharmacists
 - iv. Insert headings (e.g., Obtaining Eligibility to Prescribe Suboxone, REMS, The Impact of a REMS on Prescribing Tradename) in the prescriber and pharmacist brochure to delineate the different sections being described. As currently written, the guide does not flow well.

- v. **Attachment G (Appendix H – clean Copy)** for revisions to the Physician Brochure, “*Important Information for Physicians- Frequently Asked Questions*”
 - vi. **Attachment I (Appendix J – clean Copy)** for revisions to the Pharmacist Brochure, “*Important Information for Pharmacists-Frequently Asked Questions*”
- b. Appropriate Use Checklist is acceptable, no revisions are necessary.

5. Implementation System

- a. Revise the proposed implementation system to include the following:
 - i. Reckitt Benckiser will verify that all DATA 2000-certified physicians receive the Introduction Letter with the appended materials.
 - ii. Reckitt Benckiser will monitor compliance with the requirements to document safe use conditions through surveys of patients and prescribers, evaluations of health care utilization databases, and ongoing surveillance (sources including, but not limited to, internet, street ethnography, national databases, and surveys conducted at substance abuse treatment programs).
 - iii. Reckitt Benckiser will monitor and evaluate the implementation of the elements to assure safe use provided for under Sections B1, above, and in the manner described in the REMS supporting document, and will take reasonable steps to improve implementation of these elements to meet the goals of the REMS.

6. Timetable for Submission Assessment

The Timetable for Assessment of the REMS have been reviewed and found to be acceptable. Please see track changes for minor editorial revisions.

7. REMS Supporting Document

- a. All changes in REMS Document should be reflected in the REMS Supporting Document for consistency.
- b. Clarify and provide the “cover letter” mentioned on page 13 of the REMS Supporting Document. Although, this letter will not be part of the appended REMS materials, it should be included in your Supporting Document.
- c. The REMS Assessment Plan is to be summarized in the REMS Supporting Document and will be included in the approval letter. The REMS Assessment Plan will include, but is not limited to the following:
 - i. An evaluation of patients’ understanding of the serious risks of the Suboxone film.
 - ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
 - iii. A report on failures to adhere to distribution and dispensing requirements for the Medication Guide, and corrective actions taken to address noncompliance.
 - iv. A survey of healthcare providers’ understanding of the serious risks of Suboxone film and the need a) for appropriate patient monitoring, b) for

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- patient adherence to conditions of safe use, c) to check that patients are using the drug appropriately and making adequate progress towards treatment goals, d) to make sure prescriptions are provided in amounts commensurate with patient stability and e) the importance of psychosocial support services. Include specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
- v. An analysis to evaluate Suboxone film utilization patterns including frequency of office visits/patient/prescriber, amount dispensed in prescriptions to new patients and other indicators of adherence to practices important to safe use.
 - vi. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from signals of abuse, misuse, overdose and addiction. Surveillance should include, among other sources, reports from street ethnography programs and pediatric exposures.
 - vii. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.
- d. The methodologies and survey instruments for the proposed patient and prescriber surveys are under review. We will provide our comments once the review is completed. The proposed methodologies and survey instruments do not need to be approved at the time of the REMS approval.

123 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22410

ORIG-1

RECKITT
BENCKISER
PHARMACEUTICA
LS INC

SUBOXONE
(BUPRENORPHINE/NALOXONE
) sublingual film

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

/s/

GITA A AKHAVAN TOYSERKANI
08/06/2010