DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022410/S-004, S-017, S-018

SUPPLEMENT APPROVAL

FULFILLMENT OF POSTMARKETING REQUIREMENT

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

Attention: Bruce Paolella
Director, Regulatory Affairs

Dear Mr. Paolella:

Please refer to your Supplemental New Drug Applications (sNDAs) dated June 1, 2011, received June 2, 2011, which was refused to file on August 01, 2011, and resubmitted March 28, 2013, (S- 004), December 13, 2013, received December 13, 2013 (S-017) and December 30, 2013, received December 30, 2013, (S-018), submitted 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 June 15, and July 20, 22, and 27, 2011, March 28, April 26, May 7 and 8, June 24, August 15, September 16, and October 28, 2013, and January 24, 2014, (S-004), and January 28, 2014 (S-018), and your risk evaluation and mitigation strategy (REMS) assessment dated April 21, 2014.

Supplement S-004 proposes a revised indication to include the use of Suboxone sublingual film for the initiation of buprenorphine treatment of opioid dependence and a proposed modification to the approved risk evaluation and mitigation strategy (REMS).

Supplement S-017 provides for revisions to the **HIGHLIGHTS: USE IN SPECIFIC POPULATIONS**, **8.1: Pregnancy** and **8.3: Nursing Mothers**, and **17.1: Safe Use** sections of the Package Insert.

Supplement S-018 proposes revisions to Section 8: **USE IN SPECIFIC POPULATIONS**, and Section 12: **CLINICAL PHARMACOLOGY** of the Package Insert to include results of the recently completed study *Pharmacokinetics of Buprenorphine and Naloxone in Subjects with Mild to Severe Hepatic Impairment (Child-Pugh Classes A, B, and C), in HCV-Seropositive Subjects, and in Healthy Volunteers*, to fulfill the following Postmarketing Commitment listed in the approval letter dated August 30, 2010.

1674-2 A clinical trial to determine the effect of hepatic impairment on the pharmacokinetics of sublingual Suboxone, and to establish whether there is a differential effect on buprenorphine as compared to naloxone

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 includes 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).

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

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

Your January 28, 2014, submission contains the final report for the following postmarketing requirement listed in the August 30, 2010, approval letter.

1674-2 A clinical trial to determine the effect of hepatic impairment on the pharmacokinetics of sublingual Suboxone, and to establish whether there is a differential effect on buprenorphine as compared to naloxone.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing requirement listed in the August 30, 2010, approval letter that has not been fulfilled.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Suboxone sublingual film was originally approved on August 30, 2010 and a REMS modification was approved on August 10, 2012. 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. Your proposed modification to the REMS consists of:

- Addition of the following information to the appended REMS materials:
  - A revised indication to allow for buprenorphine to be used in both the initiation and maintenance phases of opioid dependence.
    - Limitations of use to patients physically dependent on heroin or other short-acting opioids.
  - A new warning regarding use in patients with hepatic impairment.
  - Updated language on use in pregnancy, nursing mothers, and patients with hepatic impairment.
- Updates to the appended REMS materials to reflect information on how approved buprenorphine/naloxone combination products differ from each other, how to switch between products, and recommended dosing.
- Revisions to the appended REMS materials to convey information in a clearer, more concise manner, provide greater emphasis on messages thought to be of most importance, and remove information found to be unnecessary.

- Removal of Appendix A: Obtaining Eligibility to Prescribe Suboxone

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 modified REMS, submitted on April 21, 2014, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on August 30, 2010.

There are no changes to the REMS assessment plan described in our August 30, 2010, letter.

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

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 022410 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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 022410 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022410
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022410
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

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