



NDA 022410

NDA APPROVAL

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, and 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, August 7 and 14, and November 2, 12, 24, 2009, and January 25, March 5 (2), April 29, May 17, July 21, and August 20, 23, 24, and 27, 2010.

The November 24, 2009, submission constituted a Complete Response to our August 21, 2009, Action Letter.

This new drug application provides for the use of Suboxone (buprenorphine and naloxone) sublingual film for use in the maintenance treatment of opioid dependence when used as part of a complete treatment plan to include counseling and psychosocial support.

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

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert and Medication Guide). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your April 29, 2010, submission containing final printed carton and container labels.

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.

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.

During the review of this NDA we have become aware of a placebo-controlled thorough QT study employing another buprenorphine containing product, Butrans, approved on June 30, 2010. The study indicated QT prolongation meeting the threshold for concern at buprenorphine plasma concentrations similar to those that could be achieved with Suboxone sublingual film. Therefore, Suboxone sublingual film may have the potential to cause QT prolongation at therapeutic doses that could result in increased risk for serious cardiac events, including life-threatening arrhythmias. Further, we note that patients with hepatic impairment may have delayed clearance of, and increased exposure to, buprenorphine which could lead to an increase in adverse effects, including the potential for QT prolongation.

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 identify the unexpected serious

risk of cardiac events related to your product and whether presence of hepatic impairment increases this risk. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of cardiac events, including life-threatening arrhythmias, related to the use of Suboxone sublingual film.

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

1674-1. A clinical trial to assess the risk of QT prolongation with sublingual buprenorphine, i.e., a thorough QT (tQT) trial. A comparison to methadone at typical treatment doses should be included. It is likely this trial will need to be conducted in opioid-tolerant volunteers or new entrants to opioid dependence treatment.

The timetable you submitted via email on August 6, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 30, 2011
Trial Completion:	December 31, 2014
Final Report Submission:	September 30, 2015

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.

The timetable you submitted via email on August 16, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	April 30, 2011
Trial Completion Date:	June 30, 2013
Final Report Submission:	December 30, 2013

Submit the protocol to your IND, 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.

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)). The details of the REMS requirements were outlined in our complete response letter dated August 21, 2009.

Pursuant to 505-1(f)(1), we have determined that Suboxone sublingual film can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate 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, listed in the labeling. The elements to assure safe use will inform patients of the serious risks associated with Suboxone sublingual film and the appropriate conditions of safe use and storage of Suboxone sublingual film. The elements to assure safe use will also ensure adequate clinical monitoring of patients by healthcare providers.

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 August 27, 2010, 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:

- a. An evaluation of patients' understanding of the serious risks of Suboxone sublingual film
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
- d. A survey of healthcare providers' understanding of the serious risks of Suboxone sublingual film and the:
 - i. need for appropriate patient monitoring
 - ii. need for patient adherence to conditions of safe use
 - iii. need to check that patients are using the drug appropriately and making adequate progress towards treatment goals
 - iv. need to make sure prescriptions are provided in amounts commensurate with patient stability
 - v. importance of psychosocial support services
- e. Specific measures that will be taken to increase awareness if surveys of prescribers indicate that prescriber awareness is not adequate
- f. An analysis to evaluate Suboxone sublingual 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
- g. 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 will include, among other sources, reports from street ethnography programs and pediatric exposures

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), 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.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), 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

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