

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	August 20, 2010
From	Celia Winchell, M.D., Clinical Team Leader
Subject	Cross-Discipline Team Leader Review and Review of Safety Update
NDA #	22-410
Applicant	Reckitt Benckiser
Date of Submission	Initial Submission: October 21, 2008 Complete Response Received: November 24, 2009
PDUFA Goal Date	August 30, 2010 (extended due to major amendment)
Proprietary Name / Established (USAN) names	Suboxone (buprenorphine and naloxone) sublingual film
Dosage forms / Strength	Buprenorphine 2 mg with Naloxone 0.5 mg Buprenorphine 8 mg with Naloxone 2 mg
Proposed Indication(s)	Maintenance Treatment of Opioid Dependence (b) (4)
Recommended:	<i>Approval</i>

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1 Introduction

This New Drug Application for buprenorphine and naloxone soluble film for sublingual administration was initially received on 10/21/08 and a Complete Response letter was sent on 8/21/09 citing the need for a Risk Evaluation and Mitigation Strategy (REMS) as the sole deficiency.

Suboxone (b) (4) is intended for the maintenance treatment of opioid dependence, and was developed as an alternative to Suboxone sublingual tablets (NDA 20-733, approved October 8, 2002). The dosage strengths of Suboxone (b) (4) for which marketing approval is being sought are the same as those currently approved for Suboxone sublingual tablets, and are as follows:

- Buprenorphine 2mg With Naloxone 0.5mg (herein referred to as 2/0.5 or as 2 mg)
- Buprenorphine 8mg With Naloxone 2mg (herein referred to as 8/2 or as 8 mg)

The film formulation is intended by the Applicant to be similar in efficacy to Suboxone sublingual tablets, while offering additional safety and increased compliance. Reckitt Benckiser reports that the formulation was “created for the purpose of minimizing abuse and misuse of the product, including unintended and potentially dangerous exposure in children.” Other stated goals include increasing patient compliance, minimizing counterfeiting, minimizing illegal use and diversion, and decreased product damage during transport and storage compared to sublingual tablets. The achievement of these goals is based on the use of a unit dose product and package that is child-resistant, has enhanced physical integrity, and improved coding.

The NDA rests primarily on a program of Phase 1 pharmacokinetic (PK) studies evaluating bioavailability, dose proportionality, and comparisons to Suboxone tablets, and on previous Reckitt Benckiser data submitted to the NDAs for Suboxone and Subutex tablets, encompassing data on safety and efficacy of buprenorphine sublingual solution, Suboxone and Subutex. A small open-label safety study of Suboxone (b) (4) and a small laboratory study comparing Suboxone (b) (4) to a buprenorphine-only film strip supplements these findings. No new efficacy studies were conducted for this NDA.

¹ n.b. the proposed proprietary name, “Suboxone (b) (4)” was deemed unacceptable by the Office of Surveillance and Epidemiology (OSE); nevertheless the product will be referred to by that name in this review for convenience and clarity

2 Background

Buprenorphine HCl is a narcotic analgesic which has been marketed since 1982 as Buprenex, an injectable formulation, for the treatment of moderate to severe pain. In 2002, two sublingual tablet formulations were approved for the treatment of opioid dependence: Subutex (buprenorphine only, NDA 20-732) and Suboxone (buprenorphine with naloxone intended to deter abuse², NDA 20-733). The present NDA proposes a new dosage form of the buprenorphine/naloxone combination product, in a soluble strip intended for sublingual use. The application is based on pharmacokinetic studies in naltrexone-blocked healthy volunteers; a single open-label safety study in patients already using Suboxone; a small inpatient laboratory study comparing the initiation of dosing with Suboxone (b) (4) to initiation of dosing with a buprenorphine-only film strip; as well as reference to efficacy and safety information included in Reckitt Benckiser's approved applications for Subutex and Suboxone and a review of post-marketing data and literature regarding buprenorphine products.

3 CMC/Device

General product quality considerations; facilities review and inspection; and stability data were deemed acceptable during the initial review of the application.

3.1 Other notable issues

3.1.1 Proprietary Name Review

Three proprietary names have been evaluated for this product by the Division of Medication Error Prevention Analysis (DMEPA). (b) (4)

(b) (4) DMEPA recommended that Reckitt Benckiser manage this product and the currently marketed Suboxone sublingual tablets under the name Suboxone.

Upon resubmission of the NDA, Reckitt Benckiser submitted a request for a new proprietary name, (b) (4)

(b) (4) Thus, DMEPA found the proposed name (b) (4) unacceptable, and reiterated the recommendation that both products could be managed under the same proprietary name Suboxone. Reckitt Benckiser submitted carton and container labels using this approach and DMEPA deemed them acceptable.

² Naloxone is poorly bioavailable by the sublingual route and expected to be inactive under usual conditions of use. The inclusion of naloxone with buprenorphine in the Suboxone product is designed to reduce the intravenous abuse potential of the product compared to a buprenorphine only product by precipitating withdrawal if used intravenously by individuals physically dependent on full agonists.

4 Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology/toxicology information was reviewed in this resubmission. Label changes recommended by the pharmacology/toxicology reviewer based on the initial application are documented in the original reviews and will be incorporated in labeling.

5 Clinical Pharmacology/Biopharmaceutics

No new nonclinical clinical pharmacology/biopharmaceutics information was reviewed in this resubmission. Labeling recommended by the reviewer based on the initial application are documented in the original reviews and will be incorporated in labeling.

6 Clinical Microbiology

(n/a)

7 Clinical/Statistical- Efficacy

No new efficacy studies were included in this application. There was no statistical review of the clinical data. The efficacy data and recommendations for dosing are based on the approved application for Suboxone. (b) (4)



8 Safety

The safety review for this application focused on:

1. Data generated in Reckitt Benckiser's safety study, RB-US-07-0001
2. Data generated in Reckitt Benckiser's laboratory induction study, RB-US-07-0002
3. Reckitt Benckiser's comprehensive evaluation of hepatic safety issues, comprising their evaluation of sources such as postmarketing data, literature, and clinical trial data. This review was supplemented by a review of AERS data conducted by the Office of Surveillance and Epidemiology (OSE)
4. Reckitt Benckiser's evaluation of issues related to the use of buprenorphine in pregnancy
5. Reckitt Benckiser's evaluation of information about accidental pediatric exposure, which was submitted to substantiate the public health importance of the individually-packaged strip product.

8.1 Safety Findings

Overall, no major new safety findings concerning the combination of buprenorphine and naloxone were identified in this review.

Almost all of the safety experience with the proposed new formulation was derived from a single study. This study had a number of flaws, including inadequate training of personnel conducting safety exams, inconsistent recording of findings, treatment of participants with dosing regimens not recommended in the proposed labeling, and a high drop-out rate. As a result, although no major safety concerns arose in this study, the quality of the data and their relevance to the proposed labeling are questionable. Therefore, the labeling emphasizes the experience with the approved formulations and does not include a separate tabulation of safety findings on the new formulation.

Accidental Pediatric Exposure
This new safety information, based on post-marketing experience with the approved formulations, was identified as an issue requiring a REMS, using a MedGuide to communicate with patients about medication safety in the home. Compared to other opioid analgesics, the number of accidental exposures of small children to buprenorphine is very high, considering the extent of distribution. Most patients had minor or moderate adverse events reported; no fatal cases were reported. Some authors observed that children may be inclined to suck on or chew tablets, rather than swallow them whole, which promotes buccal absorption. Because of buprenorphine's poor oral bioavailability, tablets swallowed whole would be less harmful. It should be noted that the proposed filmstrip product cannot be spit out easily and dissolves quickly. Therefore, to the extent that some cases may be mitigated by the child spitting out the tablet before full absorption, the filmstrip product could be more hazardous than the tablet. However, the unit-dose packaging will help protect against this as long as the medication is not removed from the packaging and left out. (This may occur if patients use fractions of a strip, which is apparently common practice with tablets.)

Reports of response to naloxone in pediatric exposure cases were provided. The current labeling does not provide guidance on the use of naloxone in overdose. Labeling should be revised to reflect the advice that naloxone, at higher-than-usual doses, and potentially repeated doses, may be useful in overdose.

8.1.1.1 Hepatic Safety

The potential hepatotoxicity has been a topic of concern for some time, and was identified as a deficiency in the 1/26/01 Approvable action on the NDAs for Subutex and Suboxone. A post-marketing study to define the role of buprenorphine in the development of hepatic abnormalities in opiate addicts was included as a post-marketing commitment at the time of approval. This study, being conducted by the National Institute on Drug Abuse, rather than by Reckitt Benckiser, has been slow to enroll and no results shedding light on hepatic safety are available.

As part of the original submission of this NDA, Reckitt Benckiser was asked to do a comprehensive update on the question of hepatic safety, using any sources of available information. The reviewers concluded that the current labeling should be slightly revised to

reflect the existence of reports outside the population being treated for drug dependence, and the reports of fatal cases and cases with positive dechallenge.

A study comparing hepatic safety of buprenorphine and methadone, included as a post-marketing commitment under NDAs 20-732 and 20-733, is underway under the sponsorship of the National Institute on Drug Abuse.

There is an outstanding post-marketing commitment under NDAs 20-732 and 20-733 to study the effects of hepatic impairment on the pharmacokinetics of buprenorphine/naloxone. This study has not been initiated and it will be reiterated with this approval as a post-marketing requirement for this NDA.

8.1.1.2 Study Drug Accountability/Diversion

Reckitt Benckiser has implied that this product may represent an advantage over the current tablet products with respect to diversion. No information on accountability of drug supply for clinical trials of the tablet formulation is available, because the registration studies were done under supervised administration conditions (and in some cases used a liquid formulation). Therefore, there is no basis for comparison, but there does not appear to be any reason to conclude that this formulation rendered the study drug particularly resistant to diversion.

8.1.1.3 Use in Pregnancy

Current labeling identifies Suboxone and Subutex as Pregnancy Category C, and includes the CFR-mandated statement “There are no adequate and well-controlled studies of SUBOXONE or SUBUTEX in pregnant women. SUBOXONE or SUBUTEX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.” The label describes non-clinical findings of increases in neonatal mortality in rat studies with no safety margin.

The current language describing neonatal withdrawal in infants exposed to buprenorphine *in utero* did not fully capture the range of symptoms observed. The approved labeling for the sublingual tablet products, used as base copy, described “one case” of apnea, respiratory depression and bradycardia. Other cases of this nature have been reported and the label was revised to reflect this fact.

8.1.1.4 Common Adverse Events

Reckitt Benckiser proposed to include

 (b) (4)

The film strip can be expected to be associated with systemic adverse events similar to those seen with other formulations, and, if anything, may be more irritating locally.

8.1.2 Electrocardiograms (ECGs)

No new ECG data was reviewed in the original submission of this NDA; some ECGs were collected in the pharmacokinetic studies but were expected to offer little of interest because the population consisted of healthy volunteers under naltrexone blockade. However, since the CR action was taken, the Agency has become aware of data from a Thorough QT (TQT) study comparing transdermal buprenorphine, 10 mcg/hr or 40 mcg/hr, to a moxifloxacin control, undertaken in support of the approval of NDA 21-306 (BuTrans, Purdue Pharma).

(b) (4)

Scrutiny of the submitted tables of data from the ECGs collected in the healthy volunteer studies suggests that some subjects may have experienced QT prolongation in the PK program for this application.

However, other studies have been conducted at typical addiction treatment doses, some using fairly sophisticated ECG measurements, which do not indicate a clinically significant effect of buprenorphine.

It is not yet known what the effects would be at the exposures associated with typical addiction treatment doses. Because of the known risks of untreated opiate addiction and the inconsistent findings concerning the effects of buprenorphine on cardiac conduction in doses used in addiction treatment, it seems prudent to establish whether a true clinical concern about cardiac conduction exists prior to adding labeling language which may unduly dissuade patients and providers from using this treatment.

Therefore, based on this new safety information, Reckitt Benckiser will be required to perform appropriate studies and to incorporate appropriate labeling language. Reckitt Benckiser has been informed of this and advised that one study, using the sublingual formulation of their choice, could support labeling for all three of the sublingual products in their product line.

8.1.3 Safety Update

A safety update consisting was included with this resubmission which corrected errors included in the previous submission. For example, 13 adverse events experienced by 11 patients were included in the Clinical Study Report for Study RB-US-07-0001 in the original NDA 22-410 but were not included in the summary tabulations of all Treatment Emergent Adverse Events included in the 4-month Safety Update submitted to NDA 22-410 (submitted on March 3, 2009, Serial No. 0009). The nature of the AEs did not contribute new information or change the overall conclusions, and the labeling will not change because no AE table based on this study was included.

Updated information from pharmacovigilance, literature searches, and Poison Control Center data pertaining to the currently-marketed products did not change the overall safety conclusions of the original review.

8.2 Safety Conclusions

8.2.1 Overall safety profile

The overall safety profile of this product is similar to that of the approved sublingual tablets.

9 Advisory Committee Meeting

No Advisory Committee meeting was held pertaining to this application.

10 Pediatrics

The active moiety of buprenorphine (with or without naloxone) has, and will retain, orphan designation for the treatment of opioid addiction. The sponsor's new formulation of buprenorphine falls under this designation and thus, pursuant to 21 U.S.C. 355c(g), is exempt from the pediatric study requirements under PREA.

Reckitt Benckiser has indicated that they have no firm plans for conducting pediatric studies, ^{(b) (4)}

11 Other Relevant Regulatory Issues

Suboxone (buprenorphine/naloxone sublingual tablets) and Subutex (buprenorphine sublingual tablets) were approved in 2002 subject to a risk management program that encompassed:

1. Targeted product distribution and sales monitoring
2. Active surveillance for diversion and abuse (including an advisory group to recommend interventions if problems were identified). This program was extensive, and included surveys of patients, treatment programs, and physicians, as well as a network of "street ethnographers" who collected information about illicit use of buprenorphine directly from individuals involved in the street drug trade.
3. Educational programs for patients, physicians, and pharmacists (n.b., this referred to specific labeling brochures for each of these audiences, approved as part of the labeling).

The risk management program also made reference to a requirement, legislated under the Drug Abuse Treatment Act of 2000, that Suboxone and Subutex could be prescribed for addiction treatment only by physicians who had met certain requirements (specifically, a minimum of 8 hours of training) and had obtained the proper waiver from the DEA via making appropriate notifications to the Substance Abuse and Mental Health Services Administration (SAMHSA).

Although considered an aspect of risk management for this product, aimed at ensuring safe and effective use and preventing abuse, misuse, and diversion, this feature was not administered by the manufacturer.

Based on safety information showing a growing problem with misuse and abuse of sublingual buprenorphine tablets, reflected in reports from Reckitt Benckiser's active surveillance program conducted as part of the current Risk Management Program for Suboxone and Subutex, REMS elements are required for this product to address the risk of misuse and abuse. The lack of an appropriate REMS was cited as the deficiency in the Complete Response letter.

The original Risk Management Program was developed prior to the passage of the Food and Drug Administration Amendments Act (FDAAA) and therefore is not enforceable. Concurrent with the CR action on this application, a REMS letter was sent to Reckitt Benckiser requiring submission of a REMS for the approved sublingual tablet (b) (4).

The specific safety concerns to be addressed include:

1. Accidental pediatric exposures:

Accidental pediatric exposures to Suboxone and Subutex are reported at a prescription-volume-adjusted rate that exceeds that of other narcotic analgesics. A **MedGuide** strongly communicating the need to keep buprenorphine products out of reach of children is recommended as an appropriate strategy to manage this risk.

2. Increasing reports of abuse, misuse and diversion attributed to patients who receive prescriptions with little supervision or ancillary support towards recovery from drug addiction:

The post-marketing surveillance program, particularly the "street ethnography" interviews conducted as part of the risk management program note that it is easy to obtain buprenorphine on the street and that the source is usually patients who find it very easy to get excessive supplies of buprenorphine from physicians. Although both labeling and treatment guidelines recommend supervised administration and frequent face-to-face visits, progressing to less intense supervision as treatment progresses, there are reports that physicians provide prescriptions for large supplies of medication on the first visit and do not monitor progress, compliance, or ongoing illicit drug use. Buprenorphine products have not been shown to be safe or effective when used in this manner. Therefore, **Elements to assure safe use** requiring the sponsor to ensure that patients are monitored appropriately (i.e., in keeping with labeling and SAMHSA guidelines) is recommended as a strategy to ensure safe and effective use and to prevent abuse and misuse.

Because physician certification is provided for under the Drug Abuse Treatment Act (DATA) and the responsibility for this certification has been delegated to the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Drug Enforcement Administration (DEA), it does not seem appropriate to create a separate

education and certification program to be administered by Reckitt Benckiser. However, despite this provision, it appears apparent that there is widespread disregard of the recommendations for use of the product, in terms of frequency of face-to-face visits, counseling provided, monitoring of results, and also in dosing, with many (if not most) patients receiving multiple daily doses, which are pharmacologically illogical and unsupported by efficacy data, and promote diversion by, in many cases, giving patients more tablets per prescription than would be required with a single daily dose. The objectives of this element of the REMS should be to ensure that the products are used under conditions that ensure safe and effective use, specifically ensuring that patients are monitored carefully and frequently and provided with necessary counseling, and that medication is provided to patients in appropriate doses and quantities to prevent diversion.

Because the active surveillance program already in place for Subutex and Suboxone has been useful and effective in detecting problems, this should be included as an aspect of the evaluation of the REMS.

In addition to the above information conveyed in the Complete Response letter, after extensive internal discussion, Reckitt Benckiser was provided with the advice concerning the required REMS. Note that the original REMS memo of August 2009 called for elements to assure safety use (ETASU) under 505-1(f)(3)(E), each patient using the drug to be subject to certain monitoring. However, upon further consideration and internal review, it became apparent that some of the recommended risk mitigation measures included aspects of 505-1(f)(3)(D), the drug being dispensed to patients with evidence or other documentation of safe-use conditions. In turn, this ETASU may be associated with a requirement for an implementation plan, which has been included. Therefore, per agreement between OND and OSE, the final version of the REMS will include:

- A. Medication Guide
- B. Elements to Assure Safe Use

1. Safe use conditions

- a. SUBOXONE film will only be dispensed by the prescriber or prescribed to patients with documentation of the following safe use conditions:
 - i. Verification that the patient meets the diagnostic criteria for opioid dependence.
 - ii. Risks described in the professional labeling and the Medication Guide have been discussed with the patient.
 - iii. Safe storage of the medication has been explained and reviewed with the patient.
 - iv. After appropriate induction, the patient is prescribed a limited amount of medication at the first visit.
- b. Reckitt Benckiser Pharmaceuticals Inc. will perform the items outlined in Section C.

- c. Prescribers will document safe use conditions for each patient by using the ‘Appropriate Use Checklist,’ or by using another method (e.g. electronic health record) specific to the prescriber’s office practice.³
- d. Reckitt Benckiser Pharmaceuticals Inc. will ensure that within 30 days of FDA approval of the SUBOXONE REMS, a REMS Instruction Letter to Prescribers will be mailed to all physicians certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This letter is designed to convey and reinforce the risks of accidental overdose, misuse, and abuse of SUBOXONE, as well as the need to appropriately monitor patients and document safe use conditions.
- e. Reckitt Benckiser Pharmaceuticals Inc. will, on a monthly basis, identify any newly DATA 2000-certified physicians and mail the applicable documents to them. The following materials will be appended to the Prescriber Instruction Letter: Medication Guide, Full Prescribing Information, Physician Brochure, and the Appropriate Use Checklist.
- f. To further reinforce safe use conditions, Reckitt Benckiser Pharmaceuticals Inc. will ensure that within 30 days of FDA approval of the SUBOXONE REMS, a REMS Introductory Letter for Pharmacists will be mailed to all pharmacists on a national mailing list from the American Pharmacists Association. The following materials will be appended to the Introductory Pharmacist Letter: Medication Guide, Full Prescribing Information and the Pharmacist Brochure.
- g. Reckitt Benckiser Pharmaceuticals Inc. will make the letters and all materials that are appended to the letters available through its toll-free information line, through its field personnel, and on the product website.

2. Each patient using SUBOXONE film will be subject to certain clinical monitoring

- a. Reckitt Benckiser Pharmaceuticals Inc. will assess the REMS to ensure that each patient using SUBOXONE film will be subject to the following monitoring:
 - i. Return visits are scheduled at intervals commensurate with patient stability. Weekly, or more frequent, visits are recommended for the first month.
 - ii. Assessment and reinforcement of patient’s compliance with the prescribed medication.
 - iii. Assessment of appropriateness of dosage prescribed.
 - iv. Assessment of whether patient is receiving the necessary psychosocial support.
 - v. Assessment of whether patient is making adequate progress towards treatment goals.
- b. Reckitt Benckiser Pharmaceuticals Inc. will perform the items outlined in Section C.

³ The Appropriate Use Checklist emphasizes best practices but is worded to permit clinical judgment. Both conditions necessary for safe use appropriate clinical monitoring are communicated/prompted by the Appropriate Use Checklist. See Appendix.

- c. Prescribers will document that each patient has received the required clinical monitoring using the ‘Appropriate Use Checklist,’ or by using another method/system (e.g. electronic health record) specific to the prescriber’s office practice.

The following materials are part of the REMS and are appended to the REMS document:

- SUBOXONE film Medication Guide
- REMS Instruction Letter to Prescribers
- REMS Introductory Letter to Pharmacists
- Appropriate Use Checklist
- Physician Brochure, “*Important Information for Physicians- Frequently Asked Questions*”
- Pharmacist Brochure, “*Important Information for Pharmacists-Frequently Asked Questions*”

C. Implementation System

The Implementation System includes the following:

1. Reckitt Benckiser Pharmaceuticals Inc. will ensure that all DATA 2000-certified physicians receive the Instruction Letter with the appended materials.
2. Reckitt Benckiser Pharmaceuticals Inc. will monitor compliance with the requirements to document prescribing and dispensing with documentation of 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).
3. Reckitt Benckiser Pharmaceuticals Inc. 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.

D. Timetable for Submission of Assessments

Reckitt Benckiser Pharmaceuticals Inc. will submit REMS Assessments to FDA (b) (4)

To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Reckitt Benckiser Pharmaceuticals Inc. will submit each assessment so it will be received by the FDA on or before the due date.

12 Labeling

At Agency request, Reckitt Benckiser used as base copy for the physician labeling the Suboxone/Subutex label, revised per Agency recommendations. (In some cases, Agency recommended language was modified; these instances were not all identified.) This label, however, is in PLR format and therefore comparisons to the Suboxone/Subutex label are rendered complex.

The major changes recommended to the proposed label include:

1. [REDACTED] (b) (4)
2. Addition of sections on “Clinical Supervision” and on the management of “Unstable Patients” to the *Dosage And Administration* section to more clearly convey the appropriate management of patients with this medication, including the need for careful monitoring, frequent visits, and caution concerning quantities of take-home medication. Some of this text appeared elsewhere in labeling but was moved to increase prominence.
3. Revision of a section inserted by Reckitt Benckiser entitled [REDACTED] (b) (4)
[REDACTED]
Because this was the critical safety issue, this section was retitled “Use in Opioid-Naïve Patients” and revised to provide the relevant information [REDACTED] (b) (4)
4. Revision of the *Adverse Reactions* section [REDACTED] (b) (4)
[REDACTED]
5. Reorganization of *Controlled Substance, Abuse, and Dependence* sections along the lines of other opioid drugs.
6. Restoration of a statement (which was in the text provided to Reckitt Benckiser by the Agency) noting that buprenorphine/naloxone combinations may be injected by some individuals.
7. Revision of *Nonclinical Toxicology* section to include results of studies reviewed in this application.
8. Addition of a statement about inhibition of CYP enzymes by buprenorphine.
9. [REDACTED] (b) (4)

12.1 Medication guide

A Medication Guide was included with the labeling and addresses the key safety concerns.

12.2 Physician and Pharmacist Brochures

The labeling approved for Subutex and Suboxone in 2002 included brochures aimed at physicians and pharmacists. Both brochures provided important background information on the Drug Addiction Treatment Act of 2000 and the procedures required to obtain authorization to prescribe the product. These brochures have been revised to omit obsolete references. They are no longer considered labeling and are included as part of the REMS to support implementation.

13 Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend this application be approved.

13.2 Risk Benefit Assessment

This product represents a new formulation of an approved product, offering relatively minor advantages. The more rapid dissolution may be perceived as a convenience to patients. The unit-dose packaging is likely to be an effective deterrent to accidental pediatric exposure. Pediatric exposures to the currently-marketed tablets continue to occur, but are generally without severe medical consequences.

Although the sponsor has described plans to use sophisticated methods to protect the supply chain from diversion, reports from the post-marketing surveillance program indicate that most diverted supply is from patients who share or sell parts of their own prescriptions; therefore this effort, although commendable, may have little impact. Conversely, the difficult-to-counterfeit individual packages may actually increase the street value of diverted product because product identity is ensured.

13.3 Recommendation for Postmarketing Risk Management Activities

The REMS as described above will be implemented by Reckitt Benckiser.

13.4 Recommendation for other Postmarketing Study Commitments

1. Assessment of the cardiac conduction effects of buprenorphine at plasma concentrations relevant to addiction treatment should be undertaken, ideally in comparison to methadone at doses commonly used in addiction treatment.

2. A post-marketing commitment agreed to under NDA 20-733, to study the effects of severe hepatic impairment on the pharmacokinetics of Suboxone, remains outstanding at this time and will be included as a post-marketing requirement under this NDA. Once completed, this study would satisfy both the PMR for 22-410 and the outstanding PMC.
3. Finally, post-marketing study reports of oral mucosal AEs should be monitored. The main safety study submitted in this application seems to have been inadequate to characterize the oral mucosal safety of this product. However, because the health implications of oral mucosal irritation are relatively minor, characterization in a more carefully-conducted study could occur as a post-marketing study, if deemed necessary based on AE reports.

APPENDIX
SUBOXONE® and SUBUTEX® APPROPRIATE USE CHECKLIST

Patient Name: _____

As a healthcare provider who prescribes SUBOXONE® (buprenorphine and naloxone) sublingual tablets CIII, SUBOXONE® (buprenorphine and naloxone) sublingual film, or SUBUTEX® (buprenorphine) sublingual tablets CIII, you may find this checklist a useful reminder of the safe use conditions and monitoring requirements to be addressed during each patient's appointment. These include: 1) understanding and reinforcement of safe use conditions, 2) the importance of psychosocial counseling, and 3) screening and monitoring patients to determine progress towards treatment goals.

If a patient continues to abuse various drugs or is unresponsive to treatment, including psychosocial intervention, it is important that you assess the need to refer the patient to a specialist and/or more intensive behavioral treatment environment.

Additional resource: Physician Clinical Support System: <http://www.pcssbuprenorphine.org>⁴

Measurement to Ensure Appropriate Use	Intake/ Induction	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Date:								
Induction								
Verified patient meets diagnostic criteria for opioid dependence								
Discussed risks described in professional labeling and Medication Guide with patient								
Explained or reviewed conditions of safe storage of medication								
Provided induction doses under appropriate supervision								
Prescribed limited amount of medication at first visit								
Scheduled next visit at interval commensurate with patient stability <ul style="list-style-type: none"> • weekly, or more frequent visits recommended for the first month 								
Maintenance								
Assessed and encourage patient to take medication as prescribed <ul style="list-style-type: none"> • Consider pill count/dose reconciliation 								

⁴ The PCSS is a SAMHSA-supported service which links practitioners with more experienced physicians to receive advice on all aspects of addiction treatment using buprenorphine.

SUBOXONE® and SUBUTEX® APPROPRIATE USE CHECKLIST

Measurement to Ensure Appropriate Use	Intake/ Induction	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Date:								
Maintenance (continued)								
Assessed appropriateness of dosage <ul style="list-style-type: none"> • Suboxone 12 mg –16 mg is recommended for maintenance • Doses higher than this should be an exception • The need for higher dose should be carefully evaluated 								
Assessed whether patient is receiving the psychosocial support considered necessary								
Assessed whether benefits of treatment with Suboxone outweigh risks associated with Suboxone								

Cross Discipline Team Leader Review

<p>Assessed whether patient is making adequate progress toward treatment goals</p> <ul style="list-style-type: none"> • Conduct urine drug screens as appropriate to assess use of illicit substances • Consider referral to more intensive forms of treatment for patients not making progress 								
<p>Scheduled next visit at interval commensurate with patient stability</p> <ul style="list-style-type: none"> • weekly, or more frequent visits are recommended for the first month 								

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/

CELIA J WINCHELL
08/20/2010