CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022410Orig1s000

SUMMARY REVIEW

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia and Analgesia Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	August 30, 2010
From	Rigoberto Roca, M.D. Deputy Director Division of Anesthesia and Analgesia Products
Subject	Deputy Division Director Summary Review
NDA Number	022410
Applicant Name	Reckitt Benckiser
Date of Original Submission	October 21, 2008
Date of Complete Response	August 21, 2009
Date of Re-Submission	November 30, 2009
PDUFA Goal Date	August 30, 2010 (extended due to a submission of a major amendment)
Proprietary Name / Established (USAN) Name	Suboxone (Buprenorphine/naloxone) sublingual film
Dosage Forms / Strength	Sublingual film 2 mg/0.5 mg and 8 mg/2 mg
Proposed Indication(s)	For the maintenance treatment of opioid dependence (b) (4)
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Celia Winchell, M.D.
DDMAC	Mathilda Fienkeng, Pharm.D., Regulatory Review Officer Twyla Thompson, Pharm.D., Regulatory Review Officer
OSE/DMEPA	Zachary Oleszczuk, PharmD, Acting Team Leader Denise Toyer, PharmD, Deputy Director
OSE/DRISK	Jeanne Perla, Ph.D., Risk Management Analyst; Megan Moncur, Risk Management Analyst; Gita Toyserkani, Pharm.D., Acting Team Leader; Marcia Britt, Ph.D., Health Education Reviewer; and Brian Gordon, MA., Social Science Reviewer
Office of Compliance	Agnes Plante, BSN, RN, Consumer Safety Officer

CDTL = Cross-Discipline Team Leader
DDMAC = Division of Drug Marketing, Advertising and Communication
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management
DSI = Division of Scientific Investigations
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, Reckitt Benckiser, submitted an application on October 21, 2008, for a line extension of, and as an alternative to, their Suboxone tablets. The new formulation is a sublingual strip, in dosage strengths that are similar to the approved tablets; specifically, buprenorphine 2 mg/naloxone 0.5 mg and buprenorphine 8 mg/naloxone 2 mg. The application received a Complete Response on August 21, 2009, because it did not contain an adequate Risk Evaluation and Mitigation Strategy (REMS) to address the Agency's concerns regarding misuse and abuse of the product. The Applicant's submission of November 24, 2009, constituted a Complete Response to the Action letter of August 21, 2009.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

Buprenorphine is an opioid partial agonist which has been marketed as an injectable analgesic since 1982. Subutex (buprenorphine) and Suboxone (buprenorphine and naloxone) were approved in 2002 for the treatment of opioid dependence. These products may only be prescribed by health care professionals who have fulfilled certain training requirements defined in the Drug Abuse Treatment Act of 2002, which also limits the number of patients for whom a specific health care professional or group practice may prescribe these products. As noted in Dr. Rappaport's memorandum from the first review cycle, due to its pharmacological properties, buprenorphine, with or without naloxone, has been thought to be useful only in patients with mild to moderate degrees of opioid dependence. Methadone remains the treatment of choice for patients with more severe forms of opioid addiction.

Dr. Rappaport also noted that the Applicant purportedly created this formulation to minimize abuse and misuse, including unintended exposures in children. The Applicant also posited an increase in patient compliance, minimization of counterfeiting, minimization of illegal use and diversion, and a decrease in product damage during transport and storage compared to the sublingual tablets. These goals were based on the use of unit dose packaging and child-resistant packaging with improved coding.

Support for the efficacy and safety of this product rested primarily on data from Phase 1 pharmacokinetic studies evaluating bioavailability, dose proportionality, and comparisons to Suboxone tables, and reference to the sponsor's NDAs for Suboxone and Subutex. A small open-label safety study of the buprenorphine/naloxone strip and a small laboratory study comparing the buprenorphine/naloxone strip to a buprenorphine-only strip supplemented these findings.

3. Chemistry, Manufacturing, and Controls (CMC)

All issues related to product quality, facilities review and inspections, as well as stability testing were addressed during the first review cycle. There were no outstanding issues that would have precluded approval, and no new information was submitted or reviewed with this submission.

4. Nonclinical Pharmacology/Toxicology

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

Hepatic impairment:
The Applicant has an outstanding post-marketing commitment under the NDAs for Subutex (NDA 020732) and Suboxone (NDA 020733) 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.

Thorough QT Study
As noted in Dr. Winchell's review, there were no new electrocardiographic data reviewed in the original submission. The Applicant had submitted data on electrocardiograms collected during the pharmacokinetic studies; however, these data were not expected to yield any information relevant to the application because they were collected from healthy volunteers and not in the same manner and degree were a determination could be made on the effect of the QT interval.

Since the action was taken on August 21, 2009, the Agency has become aware of the results of a thorough QT (TQT) study conducted by Purdue Pharma with their transdermal buprenorphine product (BuTrans, NDA 021306). In this study, transdermal application of buprenorphine, 10 mcg/hr and 40 mcg/hr, were compared to a moxifloxacin control. (b) (4)

Dr. Winchell also noted in her review that there have been other studies reported in the literature, conducted with buprenorphine at typical addiction treatment doses and appropriate ECG measurements, which do not indicate a clinically significant effect on the QT interval.

Outstanding or Unresolved Issues

(b) (4)

the Applicant will be required to conduct a thorough QT study. This can be accomplished as a post-approval study, and will be identified as a post-marketing requirement in the action letter.

6. Clinical Microbiology

The drug product, buprenorphine/naloxone, is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

There were no new efficacy data submitted in support of this application, and none were needed in support of the complete response submission.

8. Safety

As noted in Dr. Winchell's review of the original submission, the safety review of the application consisted of:

1. Data generated in the Applicant's safety study, RB-US-07-0001.
2. Data generated in the Applicant's laboratory induction study, RB-US-07-0002.
3. The Applicant'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. The Applicant's evaluation of issues related to the use of buprenorphine in pregnancy.
5. The Applicant's evaluation of information about accidental pediatric exposure, which was submitted to substantiate the public health importance of the individually-packaged strip product.

Dr. Rappaport's noted in his memorandum that there were no serious or unexpected safety signals identified during the first review cycle. However, three concerns were noted by the review team:

- Potential for oral mucosal irritation;
- Potential to precipitate withdrawal in the opioid dependent patients who would be treated by this product; and
- Potential for hepatotoxicity.

Dr. Rappaport noted that the incidence of withdrawal symptoms in the overall database was no higher than would be expected in this patient population, and, therefore, generally not concerning. He also noted that, while there was no new or increased hepatotoxicity signal noted in the database, the previous post-marketing commitment to evaluate the comparative effects of buprenorphine and methadone on the liver should be reiterated.

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