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APPLICATION NUMBER:

022410Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	August 21, 2009
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products
Subject	Division Director Summary Review
NDA #	22-410
Applicant Name	Reckitt Benckiser
Date of Submission	October 21, 2008
PDUFA Goal Date	August 21, 2009
Proprietary Name / Established (USAN) Name	Suboxone (Buprenorphine/naloxone) sublingual film
Dosage Forms / Strength	Sublingual films 2 mg/0.5 mg and 8 mg/2 mg
Proposed Indication	For the maintenance treatment of opioid dependence (b) (4)
Action:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Elizabeth M. Kilgore, M.D.; Celia Winchell, M.D.
Statistical Review	N/A.
Pharmacology Toxicology Review	Elizabeth A. Bolan, Ph.D. ; R. Daniel Mellon, Ph.D.
CMC Review	Xavier Ysern, Ph.D.; Ali Al-Hakim, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DDDP	Fred Hyman, D.D.S., M.P.H.; John Kelsey, D.D.S., M.B.A.; Susan Walker, M.D.
DSI	Susan Leibenhaut, M.D.; Constance Lewin, M.D.
CSS	Jian Ping, M.D., Ph.D.; Lori A. Love, M.D. Ph.D.; Michael Klein, Ph.D.
CDTL Review	Celia Winchell, M.D.
OSE/DMEPA	Zachary Oleszczuk, Pharm.D; Kellie Taylor, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph.

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DDDP=Division of Dermatology and Dental Products
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
CSS=Controlled Substance Staff
CDTL=Cross-Discipline Team Leader

1. Introduction

Reckitt Benckiser has submitted this application for a line extension of and as an alternative to their Suboxone tablets which were approved in 2002. This new formulation contains buprenorphine and naloxone in a new delivery system, sublingual strips. The dosage strengths for these strips, buprenorphine 2 mg/naloxone 0.5 mg and buprenorphine 8 mg/naloxone 2 mg, are the same as the approved tablets. The sponsor purportedly created this formulation to minimize abuse and misuse, including unintended exposures in children, in addition to increasing patient compliance, minimizing counterfeiting, minimizing illegal use and diversion, and decreasing 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 rests primarily on data from Phase 1 pharmacokinetic studies and reference to the sponsor's NDAs for Suboxone and Subutex.

2. Background

Buprenorphine is an opioid partial agonist which has been marketed as an injectable analgesic since 1982. Subutex (buprenorphine alone) and Suboxone 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. 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.

Recent data has shown increasing rates of abuse and diversion of Subutex and Suboxone. There is also an unexpectedly high rate of accidental exposure to children, thought to be due to the social dysfunction found in the homes of many opioid addicts. However, the number of deaths due to these accidental exposures has been low, again possibly due to the pharmacological properties of the drug.

The main concerns raised by the review team in regard to this new product are the need for an adequate REMS to mitigate the risks of abuse and accidental exposures to children, the need for finalization of the ongoing Subutex/Suboxone post-marketing study on hepatotoxicity, and better characterization of the mucosal safety of this product. While the clinical review team has determined that the hepatotoxicity study and the collection of additional data to support mucosal safety may be completed post-marketing, the REMS submitted by the sponsor in this application is not acceptable and, therefore, the application cannot be approved at this time.

3. CMC

The product is formulated as a sublingually applied film which hydrates to a gel form within about 30 seconds after application to the oral mucosa. The gel then erodes over approximately three minutes releasing the active components. A process impurity, (b) (4), was noted to have a structural alert for mutagenicity due to an (b) (4) functionality. An Ames test of this impurity was negative, but an in vitro cytogenetic assay in human lymphocytes showed it to be clastogenic at high dose levels. The sponsor has agreed to a specification limit reduction that is acceptable to the CMC and Pharmacology/Toxicology review teams.

The two dosage strengths of this product are produced from separate film formulations. The 2-mg/0.5-mg strength is produced from a low-strength formulation and the 8-mg/2-mg strength is produced form a high-strength formulation. Three different doses made from the high-strength formulation were used in the clinical studies, 12 mg/3 mg, 16 mg/4 mg, and the to-be-marketed 8 mg/2 mg. (b) (4)

However, as Dr. Winchell notes on page 7 of her review, (b) (4)

All manufacturing, testing and packaging facilities have been inspected. A twelve-month expiration period is supported by the submitted stability data.

4. Nonclinical Pharmacology/Toxicology

Three concerns were addressed by the pharmacology/toxicology review team:

1) Specifications for the clastogenic impurity [redacted] (b) (4): see discussion under Section 3.
2) In vitro studies conducted by the sponsor to assess the interaction of buprenorphine and its metabolite norbuprenorphine with several cytochrome P450 enzymes and to assess binding of buprenorphine and norbuprenorphine to benzodiazepine receptors due to the apparent increased toxicity noted in the clinical setting when Subutex or Suboxone are taken concomitantly with benzodiazepines. While there was some inhibition of cytochrome P450 enzymes at micromolar levels, the plasma concentrations of buprenorphine in the therapeutic range are unlikely to cause clinically significant inhibition of these enzymes. Neither buprenorphine nor norbuprenorphine were found to bind to either central or peripheral benzodiazepine receptors.
3) Benign Leydig cell adenomas were observed in a two-year carcinogenicity study of Suboxone in rats. Leydig cell adenomas were seen in a prior carcinogenicity study of buprenorphine alone in rats, but a mouse study was negative. These findings will be discussed in the product labeling.

5. Clinical Pharmacology/Biopharmaceutics

The following is reproduced form page 11 of Dr. Winchell's review:

> This overview of buprenorphine and buprenorphine/naloxone clinical pharmacology is taken largely from the approved labeling for NDA 20-723 and 20-733.
>
> Pharmacokinetics of buprenorphine and naloxone (as Suboxone) show wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability is low. Both C_{max} and AUC of buprenorphine show dose linearity in the range of 4 to 16 mg, but not dose proportionality. The table below from the labeling for Suboxone and Subutex shows the PK parameters. Buprenorphine has a mean elimination half-life of 37 hours; naloxone has a half-life of 1.1 hours. Naloxone does not affect the PK
>
> **Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone doses and 16mg Subutex dose (mean (%CV)).**

Pharmacokinetic Parameter	Suboxone 4 mg	Suboxone 8 mg	Suboxone16 mg	Subutex 16 mg
C_{max}, ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC_{0-48}, hour.ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

> Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.
>
> Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation. Cytochrome P-450 3A4 (CYP3A4) inhibitors may increase plasma concentrations of buprenorphine.

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