CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208042Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 4, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208042
Product Name and Strength:	Cassipa (Buprenorphine and Naloxone Sublingual Film) 16 mg/4 mg
Applicant/Sponsor Name:	Teva Pharmaceuticals
FDA Received Date:	August 31, 2018
OSE RCM #:	2018-561-1
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised container label and carton labeling for Cassipa (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling for Cassipa are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Schlick J. Label and Labeling Review for Cassipa (NDA 208042). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jun 28. RCM No.: 2018-561.

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/s/

JAMES H SCHLICK
09/04/2018

OTTO L TOWNSEND
09/04/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 17, 2018
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	CASSIPA (buprenorphine and naloxone) sublingual film, (CIII)
Application Type/Number:	NDA 208042
Applicant:	Teva Pharmaceuticals USA

1 INTRODUCTION

On March 8, 2018, Teva Pharmaceuticals USA submitted for the Agency's review a Class 2 Resubmission original New Drug Application (NDA) 208042 for CASSIPA (buprenorphine and naloxone) sublingual film. This 505(b)(2) Application was submitted in response to the Agency's Complete Response Letter issued on September 30, 2016 because a facility inspection could not be completed. The Reference Listed Drug for this application is NDA 022410 for SUBOXONE (buprenorphine hydrochloride and naloxone hydrochloride) sublingual film. With this submission, the Applicant is proposing an indication for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on March 27, 2018 and March 22, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CASSIPA (buprenorphine and naloxone) sublingual film.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft CASSIPA (buprenorphine and naloxone) sublingual film MG received on March 8, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 3, 2018.
- Draft CASSIPA (buprenorphine and naloxone) sublingual film Prescribing Information (PI) received on March 8, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 3, 2018.
- Approved SUBOXONE (buprenorphine hydrochloride and naloxone hydrochloride) sublingual film comparator labeling dated February 1, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
08/17/2018

NIMA OSSAREH
08/17/2018

MORGAN A WALKER
08/17/2018

LASHAWN M GRIFFITHS
08/20/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
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Food and Drug Administration
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Pregnancy and Lactation Labeling Rule (PLLR) Review

Date: 08-15-2016

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health (DPMH)

To: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: **B**uprenorphine-naloxone sublingual film NDA 208042

Applicant: Teva

Subject: Pregnancy and Lactation labeling review as part of 505 (b)(2) application

Materials Reviewed:
- Applicant's proposed labeling
- Recently finalized labeling for reference listed drug, Suboxone (action pending)
- DPMH Suboxone review (4-11-2016)
- Division of Epidemiology I (DEPI I) Suboxone reviews (3-11-2016)
- Division of Biometrics VII Suboxone review (2-10-2016)

Consult Question: Please review the sponsor's proposed labeling revisions

INTRODUCTION

On November 15, 2015 the applicant submitted a 505 (b)(2) application for a new dosage of buprenorphine-naloxone sublingual film (16 mg/4 mg), for the (b) (4) of opioid dependence. Only pharmacokinetic data were submitted to support the application. Labeling is based on the reference listed drug, Suboxone. On January 16, 2016, DAAAP consulted DPMH to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Buprenorphine is a partial mu-opioid agonist that was approved in 2002 for treatment of opioid dependence. Naloxone is an antagonist at mu-opioid receptors and produces opioid withdrawal when administered parenterally. Suboxone, the reference listed drug (RLD), is the marketed combination of buprenorphine and naloxone, administered sublingually. The combination product was developed with the intent of deterring intravenous abuse of buprenorphine, as naloxone is inactive when taken by the sublingual or oral route, but results in opioid withdrawal if injected. Other buprenorphine and buprenorphine-naloxone products with various formulations have subsequently been approved.

Management of Opioid Dependence in Pregnancy

Historically, methadone has been the standard treatment for opioid dependence in pregnancy.[1] More recently, use of buprenorphine to treat pregnant women with opioid dependence has become more common, based on an accumulating body of medical literature. An American College of Obstetricians and Gynecologists' (ACOG) Committee Opinion and the American Society of Addiction Medicine state that buprenorphine may be offered to patients in need of opioid-assisted therapy during pregnancy.[2,3] Both organizations recommend buprenorphine without naloxone during pregnancy due to limited safety data on naloxone and to avoid precipitated withdrawal in the fetus if the product is injected.

Labeling of Suboxone, the RLD

During the recent pregnancy efficacy supplement review for Suboxone, pregnancy labeling was revised (finalized internally by DAAAP 7-26-2016, pending a final action) following a review of available randomized controlled trials and observational studies by DPMH, the Division of

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[1] Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. Treatment improvement protocol series 43. Substance Abuse and Mental Health Services Administration; 2005, revised 2012. Available at: http://www ncbi.nlm.nih.gov/books/NBK26113.

[2] American College of Obstetricians and Gynecologists Committee Opinion Opioid Abuse, Dependence, and Addiction in Pregnancy. Number 524, May 2012.

[3] American Society of Addiction Medicine National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use 2015.

Epidemiology I (DEPI I), and the Division of Biometrics VII (DB VII).[4] Pregnancy labeling was revised to include risk statements that state that available randomized controlled studies and observational studies were not designed appropriately to assess the risk of major malformations. These statements were added to the existing risk statement that available limited data on buprenorphine use in pregnancy do not show an increased risk of major malformations. In addition, a summary of available data and a description of the limitations were added under the Human Data section.

Revisions to the Clinical Considerations section included the addition of a statement on the risk of relapse under the "Disease associated risk" heading, the possible need to adjust the dose during pregnancy under the "Dose Adjustment during Pregnancy and the Postpartum Period" heading, and the possible need for additional analgesia during labor under the "Labor or Delivery" heading.

Subsection 8.3 Females and Males of Reproductive Potential was added by DAAAP in order to include class labeling of infertility information for chronic opioid use based on post-marketing reports.

Labeling Language for neonatal opioid withdrawal syndrome (NOWS)

The Agency implemented safety labeling changes related to neonatal opioid withdrawal syndrome (NOWS) for extended-release/long-acting (ER/LA) opioid analgesics on September 10, 2013. Following a citizen petition from the National Advocates for Pregnant Women on October 17, 2013, objecting to the changes, the NOWS labeling language was revised on April 16, 2014 to state that NOWS is potentially life-threatening if not recognized and treated.[5] To discuss issues raised by the Citizen Petition and stakeholders regarding labeling of opioids approved for treatment of addiction, the Agency convened the Risk Communication Advisory Committee in June 2015 for recommendations regarding effective communication strategies. DPMH has participated in ongoing discussion of labeling of NOWS and pregnancy labeling of addiction products and opioids, taking risk-benefit into consideration. In order to appropriately inform prescribers about the risks of NOWS without inadvertently discouraging treatment for pregnant women with opioid addiction, NOWS language for buprenorphine and methadone products was revised on 5-26-2016.[6]

[4] See following reviews in DARRTS: DPMH review dated 4-11-2016, DEPI I reviews dated 3-11-2016, and DBV VII review dated 2-10-2016.

[5] On 3-22-2016 the Agency implemented safety labeling changes that included the addition of NOWS language to Immediate Release (IR) opioid analgesics.

[6] FDA Safety Labeling Changes.Neonatal opioid withdrawal syndrome and medication-assisted treatment with methadone and buprenorphine. 5-26-2016.
http://www fda.gov/drugs/drugsafety/ucm503630.htm

Pregnancy and Lactation Labeling Rule (PLLR)

The Pregnancy and Lactation Labeling Rule (PLLR) went into effect on June 30, 2015.[7] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION AND CONCLUSIONS

DPMH revised subsections 5.5, 8.1, 8.2, and 8.3 of the buprenorphine-naloxone labeling for compliance with PLLR, based on recently finalized labeling for Suboxone, the RLD (see below). The only additional labeling revision that DPMH made is the addition of the following statement to the background risk statements under the Pregnancy Risk Summary heading, based on new advice from the PLLR Policy working group:

“ (b) (4) ”.

See final labeling for all of the labeling revisions negotiated with the applicant.

DPMH LABELING RECOMMENDATIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------WARNINGS AND PRECAUTIONS----------

- Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy (5.5)

FULL PRESCRIBING INFORMATION

5.5 Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly *[see Use in Specific Populations (8.1)]*.

Advise pregnant women receiving opioid addiction treatment with (b) (4) of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be

[7] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

available *[see Use in Specific Populations (8.1)]*. This risk must be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance and benefits of management of opioid addiction throughout pregnancy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data on use of buprenorphine in pregnancy are limited; however, these data do not indicate an increased risk of major malformations specifically due to buprenorphine exposure. There are limited data from randomized clinical trials in women maintained on buprenorphine that were not designed appropriately to assess the risk of major malformations *[see Data]*. Observational studies have reported on congenital malformations among buprenorphine-exposed pregnancies, but were also not designed appropriately to assess the risk of congenital malformations specifically due to buprenorphine exposure *[see Data]*. The extremely limited data on sublingual naloxone exposure in pregnancy are not sufficient to evaluate a drug-associated risk.

Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant and higher doses. Embryo-fetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 6 and 0.3 times, respectively, the human sublingual dose of 16 mg/day of buprenorphine. Pre-and postnatal development studies in rats demonstrated increased neonatal deaths at 0.3times and above and dystocia at approximately 3 times the human sublingual dose of 16 mg/day of buprenorphine. No clear teratogenic effects were seen when buprenorphine was administered during organogenesis with a range of doses equivalent to or greater than the human sublingual dose of 16 mg/day of buprenorphine. However, increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 0.6 (b) (4) (b) (4) the human sublingual dose of 16 mg/day of buprenorphine.

(b) (4)

(b) (4) The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

Dose Adjustment during Pregnancy and the Postpartum Period

Dosage adjustments of buprenorphine (b) (4) may be required during pregnancy, even if maintained on a stable dose prior to pregnancy. Withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary.

Fetal/neonatal adverse reactions

Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with (b) (4).

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.(b) (4))]*.

Labor or Delivery

Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

Data

Human Data

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited data from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy do not indicate an increased risk of major malformations specifically due to buprenorphine. Several factors may complicate the interpretation of investigations of the children of women who take buprenorphine during pregnancy, including maternal use of illicit drugs, late presentation for prenatal care, infection, poor compliance, poor nutrition, and psychosocial circumstances. Interpretation of data is complicated further by the lack of information on untreated opioid-dependent pregnant women, who would be the most appropriate group for comparison. Rather, women on another form of opioid medication-assisted treatment, or women in the general population are generally used as the comparison group. However, women in these comparison groups may be different from women prescribed buprenorphine-containing products with respect to maternal factors that may lead to poor pregnancy outcomes.

In a multicenter, double-blind, randomized, controlled trial ("MOTHER") designed primarily to assess neonatal opioid withdrawal effects, opioid-dependent pregnant women were randomized to buprenorphine (n=86) or methadone (n=89) treatment, with enrollment at an average gestational age of 18.7 weeks in both groups. A total of 28 of the 86 women in the buprenorphine group (33%) and 16 of the 89 women in the methadone group (18%) discontinued treatment before the end of pregnancy.

Among women who remained in treatment until delivery, there was no difference between buprenorphine-treated and methadone-treated groups in the number of neonates requiring NOWS treatment or in the peak severity of NOWS. Buprenorphine-exposed neonates required less

morphine (mean total dose, 1.1 mg vs. 10.4 mg), had shorter hospital stays (10.0 days vs. 17.5 days), and shorter duration of treatment for NOWS (4.1 days vs. 9.9 days) compared to the methadone-exposed group. There were no differences between groups in other primary outcomes (neonatal head circumference,) or secondary outcomes (weight and length at birth, preterm birth, gestational age at delivery, and 1-minute and 5-minut e Apgar scores), or in the rates of maternal or neonatal adverse events. The outcomes among mothers who discontinued treatment before delivery and may have relapsed to illicit opioid use are not known. Because of the imbalance in discontinuation rates between the buprenorphine and methadone groups, the study findings are difficult to interpret.

Animal Data

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone during the period of organogenesis. Following oral administration to rats (b) (4), no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day (b) (4) (estimated exposure approximately 150 times (b) (4) the (b) (4) human (b) (4) sublingual dose of 16 mg) in the presence of maternal toxicity (mortality). Following oral administration to rabbits, no teratogenic effects were observed at buprenorphine doses up to 40 mg/kg/day (estimated exposure approximately 50 times the human sublingual dose of 16 mg) in the absence of clear maternal toxicity. No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the (b) (4) human (b) (4) sublingual dose of 16 mg). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Maternal toxicity was seen in the high-dose group but not at the lower doses where the findings were observed. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the (b) (4) human sublingual dose of 16 mg). In the rabbit, increased post implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day. Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the human sublingual dose of 16 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the human sublingual dose of 16 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the human sublingual dose of 16 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the human (b) (4) sublingual dose of 16 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the human sublingual dose of 16 mg), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the human (b) (4) sublingual dose of 16 mg) in the absence of

maternal toxicity or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the human sublingual dose of 16 mg) were not statistically significant. In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the human daily sublingual dose of 16 mg). No maternal toxicity was noted at doses causing post-implantation loss in this study.

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine from Gestation Day 14 through Lactation Day 21 at 5 mg/kg/day (approximately 3 times the human sublingual dose of 16 mg). Fertility, pre-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the human (b) (4) sublingual dose 16 mg (b) (4)), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the human sublingual dose of 16 mg), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the human sublingual dose of 16 mg). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the human sublingual dose of 16 mg).

8.2 Lactation

Risk Summary

Based on two studies in 13 lactating women maintained on buprenorphine treatment, buprenorphine and its metabolite norbuprenorphine were present in low levels in human milk, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is limited. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for buprenorphine- (b) (4) and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Clinical Considerations

Advise breastfeeding women taking buprenorphine products to monitor the infant for increased drowsiness and breathing difficulties.

Data

Data were consistent from two studies (N=13) of breastfeeding infants whose mothers were maintained on sublingual doses of buprenorphine ranging from 2.4 to 24 mg/day, showing that the infants were exposed to less than 1% of the maternal daily dose.

In a study of six lactating women who were taking a median sublingual buprenorphine dose of 0.29 mg/kg/day (b) (4) 5 to 8 days after delivery, breast milk provided a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, equal to 0.2% and 0.12%, respectively, of the maternal weight-adjusted dose (relative dose/kg (%) of norbuprenorphine was calculated from the assumption that buprenorphine and norbuprenorphine are equipotent).

Data from a study of seven lactating women who were taking a median sublingual buprenorphine dose of 7 mg/day an average of 1.12 months after delivery indicated that the mean milk concentrations (C_{avg}) of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the study data, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean absolute infant dose (AID) of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, or a mean relative infant dose (RID) of 0.38% and 0.18%, respectively, of the maternal weight-adjusted dose.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2)]*.

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/s/

LEYLA SAHIN
08/15/2016

LYNNE P YAO
08/16/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 8/16/18

To: Swati Patwardhan
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Nima Ossareh, PharmD, RAC Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for CASSIPA sublingual film (buprenorphine and naloxone) for sublingual use CIII

NDA: 208042

In response to DAAAP consult request dated March 22, 2018, OPDP has reviewed the proposed product labeling (PI) for CASSIPA sublingual film (buprenorphine and naloxone) for sublingual use CIII.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on August 3, 2018, and are provided below.

MG: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

48 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NIMA OSSAREH
08/16/2018

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 28, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208042
Product Name and Strength:	Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg
Product Type:	Multi-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals
FDA Received Date:	March 8, 2018
OSE RCM #:	2018-561
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Teva's Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg, (NDA 208042) for areas of vulnerability that could lead to medication errors. DAAAP requested this review as part of their evaluation of resubmission of this 505(b)(2) Application for this product. The reference listed drug (Suboxone Sublingual Film NDA 022410) was approved in August 2010.

2 REGULATORY HISTORY

We previously reviewed the pouch labels, carton labeling, Prescribing Information, and Medication Guide in OSE Review# 2015-2676 and 2015-2676-1.[a,b] Our pouch label and carton comments were conveyed to the Sponsor and we found the revised container labels acceptable in 2015-2676-1. We did not have any Prescribing Information or Medication Guide comments to convey to the Sponsor at that time. A Complete Response Letter for the Application was sent on September 30, 2016.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C N/A
FDA Adverse Event Reporting System (FAERS)*	D N/A
Other	E N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 CONCLUSION

Our evaluation of the proposed packaging, label and labeling identified one area of concern. See Section 4.1 for our recommendation.

[a] Schlick, J. Label and Labeling Review for Buprenorphine and Naloxone (Teva) NDA 208042. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 APR 28. RCM No.:2015-2676.

[b] Schlick, J. Label and Labeling Review Memorandum for Buprenorphine and Naloxone (Teva) NDA 208042. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 6. RCM No.:2015-2676-1.

4.1 Recommendation for Teva Pharmaceuticals

1. Revise the container label and carton labeling to include the proprietary name for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Buprenorphine and Naloxone that Teva Pharmaceuticals submitted on March 8, 2018, and the listed drug (LD).

Table 2. Relevant Product Information for Buprenorphine and Naloxone Sublingual Film (Teva) and the Listed Drug		
Product Name	**Buprenorphine and Naloxone Sublingual Film (Teva)**	**Suboxone Sublingual Film**
Initial Approval Date	N/A	August 30, 2010
Active Ingredient	Buprenorphine and Naloxone	Buprenorphine and Naloxone
Indication	(b) (4) of opioid dependence	Treatment of opioid dependence
Route of Administration	Sublingual	Sublingual and Buccal
Dosage Form	Sublingual Film	Sublingual Film
Strength	Proposed under ANDA 205299 and 205806: 2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; 12 mg/3 mg Proposed under NDA 208042: 16 mg/4 mg	2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; 12 mg/3 mg
Dose and Frequency	(b) (4)	Day 1 induction – up to 8 mg/2 mg per day in divided doses over 2 hour intervals Day 2 induction – Single daily dose of up to 16 mg/4 mg Maintenance dose – 4 mg/1 mg to 24 mg/6 mg once daily
How Supplied	Orange rectangular film	Orange rectangular film
Storage	Room temperature	Room temperature
Container Closure	Child-resistant polyester/foil laminated pouch; 30 films per carton	Child-resistant polyester/foil laminated pouch; 30 films per carton

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 29, 2018, we searched the L:drive and AIMS using the terms, buprenorphine, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 2 previous reviews, and we confirmed that our previous recommendations were implemented or considered.

Table 3. Summary of Previous DMEPA Reviews for Buprenorphine and Naloxone

OSE RCM #	Review Date	Summary of Recommendations
2015-2676 and 2015-2676-1	April 28, 2016 and June 6, 2016	We provided pouch label and carton labeling recommendations to minimize the risk for medication errors. We found the revised pouch labels and carton labeling acceptable in OSE No. 2015-2676-1.

APPENDIX C. N/A ISMP NEWSLETTERS
APPENDIX D. N/A FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)
APPENDIX E. N/A OTHER

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Buprenorphine and Naloxone labels and labeling submitted by Teva Pharmaceuticals on March 8, 2018.

- Container label
- Carton labeling
- Medication Guide
- Prescribing Information (Image not shown)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK
06/28/2018

OTTO L TOWNSEND
06/29/2018

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 12, 2016

To: Sharon Hertz, M.D., Director
Division of Analgesics, Anesthesia, and Addiction

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Jovita Randall-Thompson, Ph.D., Pharmacologist
Controlled Substance Staff

Alan Trachtenberg, M.D., MPH, Medical Officer
Controlled Substance Staff

Subject: Buprenorphine and Naloxone Sublingual Film - NDA 208042
Generic Name (Trade Name): buprenorphine hydrochloride and naloxone hydrochloride sublingual film
Dosage: 16 mg/4 mg of buprenorphine/naloxone; single dose per day
Formulations: 16 mg/4 mg buprenorphine/naloxone sublingual films
Route: sublingual
NDA/IND Number(s): IND 118625
Indication(s): For the (b) (4) of opioid dependence.
Sponsor: Teva Pharmaceuticals

Materials Reviewed:

- NDA 208042/ Module 1.11.4 Evaluation of abuse deterrence for buprenorphine/naloxone
- NDA 208042/ Module 3.2.P.1 Description and Composition
- NDA 208042/ Module 1.14.1.3 Labeling/ Medication Guide,
- NDA 208042/Module 5.3.1.2 Phase 1 Study Report 3007599, November 19, 2015

Table of Contents

I. Summary

1. Background

This memorandum responds to a consult dated December 7, 2015, from the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP). The consult pertains to a new drug application (NDA), for a buprenorphine (BUP) and naloxone (NAL) combination product, 16 mg BUP and 4 mg NAL sublingual film submitted under NDA 208042 by Teva Pharmaceuticals. DAAAP requested that CSS review the NDA from a controlled substance and abuse potential perspective.

Teva Pharmaceuticals is seeking approval of the16/4 mg BUP/ NAL sublingual film as treatment for the management of opioid dependence. (b) (4) During maintenance (generally Day 3 and onwards), the recommended target dosage is 16 mg BUP and 4 mg NAL day, which is given daily in a single dosage form by administering the 16/4 mg BUP/ NAL sublingual film.

Teva Pharmaceuticals submitted the16 mg/4 mg BUP/ NAL sublingual film under section 505(b)(2) on December 30, 2015, referencing Suboxone® sublingual film, for sublingual or buccal use (NDA #022410/Indivior Inc., a subsidiary of RB, formally known as Reckitt Benckiser), approved 08/30/2010). Suboxone® is approved for opioid dependence, (b) (4). Suboxone® films are formulated in the dosage strengths: 2 mg BUP with 0.5 mg NAL, 4 mg BUP with 1 mg NAL, 8 mg BUP with 2 mg NAL, and 12 mg BUP with 3 mg NAL, and is not offered as 16 mg BUP with 4 mg NAL. According to the Sponsor, the present submission of the16/4 mg BUP/ NAL sublingual film, is a new dosage form, but has an equivalent film formulation to that of Suboxone® films.

Buprenorphine formulations indicated for opioid dependence are approved for in-office treatment and are subject to provisions under the federal Drug Addiction Treatment Act of 2000 (DATA 2000, 21 U.S.C. 823(g)), this includes Suboxone® sublingual film. Under DATA, the prescription use of this product for opioid dependence is limited to only those physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence. Physicians are assigned a unique identification number that must be included on every prescription.

In the current application, study findings for the efficacy/safety of the16/4 mg BUP/ NAL sublingual film is supported by one in vivo bioequivalence study (#3007599) that established the bioequivalence of 16/4 mg sublingual film with Suboxone® (2 units of Suboxone® 8/2 mg BUP/NAL film), when both are administered sublingually. In addition, at the recommendation of the FDA in the pre-IND written response dated 30 May 2014 (Module 1.6.3, pre-IND written response 30 May 2014), Teva conducted 2 additional pharmacokinetic

studies that evaluated the effects of beverage temperature (Study 4001650) and beverage pH (Study 4001651) on the relative bioavailability of the16/4 mg BUP/NAL sublingual film.

The primary basis of our conclusions and recommendation are derived from our evaluation of Teva's abuse liability assessment of their 16 mg/4 mg sublingual film submitted under the NDA (Module 1.11.4 Evaluation of abuse deterrence for buprenorphine/naloxone), and an assessment of the abuse-related treatment emergent adverse event findings collected in the in vivo bioequivalence study (#3007599).

2. Conclusions

1. Teva Pharmaceuticals'16/4 mg BUP/ NAL sublingual film is a buprenorphine/naloxone formulation indicated for the (b) (4) of opioid dependence submitted under a 505(b)(2) NDA application.

2. Buprenorphine is an opioid agonist and is a categorized by the Drug Enforcement Administration (DEA) as a Schedule III (CIII) drug under the Controlled SubstanceS Act (CSA), whereas naloxone is an opioid antagonist and is a non-scheduled substance. Therefore, due to the presence of buprenorphine, the combination product is a CIII drug.

3. From an abuse perspective there were no measurable differences in the pharmacokinetic and the abuse-related AE profiles of Teva Pharmaceutical's16/4 mg BUP/ NAL sublingual film and Suboxone® when taken sublingually.

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. The language proposed for the product label on the risks of abuse and dependence, including Section 9.0 (b) (4), should be same as what is currently written in the existing label of Suboxone® and other buprenorphine/naloxone products taken sublingually and indicated for opioid dependence, assuming that there are no additional unforeseen outcomes in the clinical trials.

II. Discussion

Teva Pharmaceuticals'16/4 mg BUP/ NAL sublingual film is a combination product containing buprenorphine hydrochloride (HCl), a partial mu-receptor agonist and naloxone hydrochloride (HCl), a full mu-receptor antagonist. Buprenorphine (BUP) is a Schedule III (CIII) substance under the Controlled Substances Act; naloxone (NAL) is not scheduled, thus due to buprenorphine the 16/4 mg BUP/ NAL sublingual film is controlled as a CIII drug.

The reference product, Suboxone® sublingual film, is approved for the induction and maintenance treatment of opioid dependence (first approved under the discontinued Suboxone® sublingual tablet form, generic BUP/NAL sublingual tablets are still available). For the purpose of abuse, if Suboxone® sublingual film is dissolved into an injectable solution as a means to inject buprenorphine, either intravenously, subcutaneously or intramuscularly, naloxone's antagonistic effects block some of buprenorphine's agonistic effects; this in turn can cause more symptoms of withdrawal in most opioid dependent users. Such effects however are not typically manifested in non-opiate dependent users. Also it is important to note that, full antagonism of buprenorphine by naloxone is limited due to the 4:1 BUP/NAL dose ratio of Suboxone® and due to buprenorphine's higher binding affinity

for the mu receptor than naloxone, which results in buprenorphine's stronger bond to mu and ultimately buprenorphine's harder displacement from the mu receptor by naloxone. Teva Pharmaceuticals'16/4 mg BUP/ NAL sublingual film has the same abuse profile as Suboxone®, however it is recommended only for sublingual administration.

1. Chemistry

Teva Pharmaceuticals'16 mg/4 mg BUP/ NAL active pharmaceutical ingredient is buprenorphine HCl (BUP), chemical name is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride (molecular formula C_{29} H_{41} NO_4 • HCl; molecular weight is 504.10).

It also contains naloxone HCl dihydrate is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dehydrate (molecular formula $C_{19}H_{21}NO_4$ • HCl • $2H_20$; molecular weight is 399.87). It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether (Teva's 16/4 mg BUP/ NAL sublingual film draft label). Naloxone has no clinically significant effect when administered by the sublingual route, although blood levels of the drug are measurable at treatment doses.

1.1 Substance information

Teva's16/4 mg BUP/ NAL sublingual film that contains buprenorphine (BUP), a partial μ-agonist, (blocks and activates) and a κ-antagonist (blocks activity) (for review, see Lutfy & Cowan, 2004), which has little or no agonist properties at κ-receptors (Zhu et al., 1997; Toll et al., 1998) and no agonist actions at the δ-receptors (Toll et al., 1998).

As described in the currently approved Suboxone® sublingual film label (as well as the medication guide), Suboxone® is formulated in a 4:1 ratio, BUP:NAL. Teva's 16/4 mg BUP/ NAL sublingual film is also formulated in a 4:1 ratio. The film is formulated in strengths of 16 mg BUP with 4 mg NAL.

As proposed by the Sponsor and presented in the draft label, (b) (4) a target dose of 16/4 mg BUP/NAL a day as a single dose is recommended. (b) (4)

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2. Absorption, Distribution, Metabolism, Elimination (ADME)

Buprenorphine displays poor oral bioavailability. However, its bioavailability improves when it is administered sublingually. (For Suboxone®, the same holds for buccal administration). The absolute bioavailability of Teva's 16/4 mg BUP/ NAL sublingual film ranged from 46 to 65%. However, total systemic exposure to naloxone following pretreatment with low pH and high pH beverages was reduced by 24% and increased by 88%, respectively, and systemic exposure to total naloxone was reduced approximately 21% following pretreatment of the oral cavity with a hot beverage.

The mean elimination half-life of sublingually administered buprenorphine is 37 hours (Clinical Pharmacology Online). Based on studies performed with Teva's 16/4 mg BUP/ NAL sublingual film, the mean plasma elimination half-life of buprenorphine (b) (4) to (b) (4) hours and naloxone has a mean elimination half-life from plasma ranging from (b) (4) o (b) (4) hours (Teva's 16/4 mg BUP/ NAL sublingual film draft label).

3. Adverse event profile through all phases of development

Abuse-related TEAEs were reported in Phase 1 in vivo bioequivalence study (#3007599).

Specifically, the review assesses those AEs reported with the final dosage formulation in subjects that had no prior history of substance abuse or treatment (including for alcohol) within the previous 2 years and were not opioid-dependent prior to the study. Naltrexone 50 mg (1 tablet) was administered at approximately 12 hours and 0.5 hours prior to each dose of study medication, and at about 12 and 24 hours post dose.

Only Phase 1 Study #3007599 contained comparisons between Teva's 16 mg/4 mg BUP/ NAL sublingual film and Suboxone (2 x 8 mg/2 mg) and/or no treatment (pre-dose). Of the 79 subjects receiving each product in a cross-over fashion, euphoric mood was reported by 5 subjects after Suboxone, and by 1 (1.3%) other subject after only the Teva product. Six (7.6%) reported somnolence after Suboxone, while only 3(3.8%) described this after the Teva film. However, 3 also reported somnolence pre-dose as well. One of those subjects reported somnolence in all 3 conditions and one under both drug conditions. Table 1, below, shows all adverse events that are characteristic of abuse and/or affecting ability to drive or operate machinery or impair mental ability.

Table 1: Adverse Events That Are Characteristic of Abuse and/or Affecting Ability to Drive or Operate Machinery or Impair Mental Ability

Preferred term	Study 3007599 (N=80)		
	Predose (N=80) n (%)	A: bup +nal[b] (N=79) n (%)	B: SUB[c] (N=79) n (%)
Disorientation	0 (0)	0 (0)	0 (0)
Disturbance in attention	0 (0)	3 (3.8)	0 (0)
Dizziness	1 (1.3)	15 (19.0)	15 (19.0)
Energy increased	0 (0)	1 (1.3)	1 (1.3)
Euphoric mood	0 (0)	1 (1.3)	5 (6.3)
Feeling jittery	0 (0)	1 (1.3)	1 (1.3)
Gait disturbance	0 (0)	1 (1.3)	0 (0)
Hypervigilance	0 (0)	0 (0)	1 (1.3)
Illusion	0 (0)	0 (0)	2 (2.5)
Somnolence	3 (3.8)	3 (3.8)	6 (7.6)
Tremor	0 (0)	0 (0)	2 (2.5)

No other abuse-related AEs were reported. The majority of the abuse-related AEs reported with Teva's16 mg/4 mg BUP/ NAL sublingual film were below 5%. In addition, the counts of abuse-related AEs reported with Teva's16 mg/4 mg BUP/ NAL sublingual film tended to be lower than the AE counts reported with Suboxone®.

4. Safety profile

From an abuse perspective, there were no overdoses, untended pediatric exposure or suicidality or homicidal incidences reported in any of the PK/BE and clinical studies conducted under the current submission.

4.1 Evidence of abuse, misuse and diversion in clinical trials

For Study 3007599 (and beverage temperature/Study 4001650) and beverage pH/Study 4001651), participant access to Teva's16/4 mg BUP/ NAL sublingual film was limited. The administration of Suboxone was carried out by a nurse. The nurse placed each soluble film or tablet in the subject's mouth and recorded the number films and tablets applied; thus, at no time were subjects given the 16/4 mg BUP/ NAL sublingual film to administer on their own.

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/s/

JOVITA F RANDALL-THOMPSON
08/09/2016

ALAN I TRACHTENBERG
08/10/2016

MICHAEL KLEIN
08/11/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 6, 2016
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208042
Product Name and Strength:	Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg
Submission Date:	May 25, 2016
Applicant/Sponsor Name:	Teva Pharmaceuticals
OSE RCM #:	2015-2676-1
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products requested that we review the revised pouch label and carton labeling for Buprenorphine and Naloxone (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

While revising the pouch label and carton labeling, Teva changed the color of the strength presentation (b) (4)). We find this color change acceptable. Teva also made revisions to the pouch label and carton labeling based on our recommendations, and we find these

[1] Schlick J. Label and Labeling Review for Buprenorphine and Naloxone (NDA 208042). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 APR 28. 8 p. OSE RCM No.: 2015-2676.

revisions acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

JAMES H SCHLICK
06/06/2016

BRENDA V BORDERS-HEMPHILL
06/06/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 28, 2016
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 208042
Product Name and Strength:	Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg
Product Type:	Multi-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Pharmaceuticals
Submission Date:	November 30, 2015
OSE RCM #:	2015-2676
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Teva's Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg, (NDA 208042) for areas of vulnerability that could lead to medication errors. DAAAP requested this review as part of their evaluation of the 505(b)(2) submission for this product. The reference listed drug (Suboxone Sublingual Film NDA 022410) was approved in August 2010.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A C
ISMP Newsletters	N/A D
FDA Adverse Event Reporting System (FAERS)*	N/A E
Other	N/A F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Teva's proposed product is a higher strength than that of the strengths approved for Suboxone (See Appendix A). Teva proposes to market this buprenorphine and naloxone sublingual film for maintenance treatment. Because the target dosage of buprenorphine/naloxone SL film maintenance treatment is usually 16 mg/4 mg and doses can be as high as 24 mg/6 mg per day. We find the introduction of the new proposed higher strength acceptable from a medication error perspective.

However, we identified some areas of the pouch label and carton labeling that can be optimized to mitigate medication errors. These areas include increasing the prominence of the strength statement (i.e. "16 mg/4 mg"), removing the instructions on (b) (4) , and including the statement "For maintenance treatment" on the principal display panel of the carton labeling. We provide recommendations in Section 4.1 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

We recommend that Teva remove information that is not pertinent to the proposed indication and dose, and increase the readability and prominence of important information in the proposed container labels and carton labeling to promote the safe use of the product. We provide recommendations to Teva in Section 4.1 to address these concerns.

4.1 RECOMMENDATIONS FOR TEVA PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. Pouch Label and Carton Labeling

1. Remove the instructions about [redacted] (b) (4) .
2. Increase the font size of the strength statement (i.e. "16 mg/4 mg") on the principal display panels to increase the prominence of this important information.
3. Include the lot number and expiration date on the pouch label and carton labeling.

B. Carton Labeling

1. Include the following statement, "For Maintenance Treatment", on the principal display panel to increase the prominence that the indication for this strength is for maintenance dosing.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Buprenorphine and Naloxone that Teva Pharmaceuticals submitted on November 30, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Buprenorphine and Naloxone Sublingual Film (Teva) and the Listed Drug

Product Name	**Buprenorphine and Naloxone Sublingual Film (Teva)**	**Suboxone Sublingual Film**
Initial Approval Date	N/A	August 30, 2010
Active Ingredient	Buprenorphine and Naloxone	Buprenorphine and Naloxone
Indication	(b) (4) of opioid dependence	Treatment of opioid dependence
Route of Administration	Sublingual	Sublingual and Buccal
Dosage Form	Sublingual Film	Sublingual Film
Strength	Proposed under ANDA 205299 and 205806: 2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; 12 mg/3 mg Proposed under NDA 208042: 16 mg/4 mg	2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; 12 mg/3 mg
Dose and Frequency	(b) (4)	Day 1 induction – up to 8 mg/2 mg per day in divided doses over 2 hour intervals Day 2 induction – Single daily dose of up to 16 mg/4 mg Maintenance dose – 4 mg/1 mg to 24 mg/6 mg once daily
How Supplied	Orange rectangular film	Orange rectangular film
Storage	Room temperature	Room temperature
Container Closure	Child-resistant polyester/foil laminated pouch; 30 films per carton	Child-resistant polyester/foil laminated pouch; 30 films per carton

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 24, 2016, we searched the L:drive and AIMS using the terms "Suboxone".

B.2 Results

Our search identified 3 previous reviews. [1,2,3] We read the reviews to inform our overall assessment of this 505 (b)(2)review.

[1] Brahmbhatt, M. Label and Labeling Review for Suboxone (buprenorphine and naloxone) sublingual film (NDA 022410/S-020). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 DEC 8, 2014. 18 p. OSE RCM No.: 2014-1214.

[2] Borders-Hemphill V. Label and Labeling Review for Suboxone (buprenorphine and naloxone) sublingual film (NDA 022410/S-004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 DEC 13. 6 p. OSE RCM No.: 2013-1816.

[3] Mena-Grillasca C. Label and Labeling Review for Suboxone (buprenorphine and naloxone) sublingual film (NDA 022410). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 MAR 26. 22 p. OSE RCM No.: 2012-577.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Buprenorphine and Naloxone Sublingual Film labels and labeling submitted by Teva.

- Container label – October 29, 2014
- Carton labeling – October 29, 2014
- Prescribing Information – No image – November 30, 2015
- Medication Guide – No image – November 30, 2015

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[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JAMES H SCHLICK
04/28/2016

BRENDA V BORDERS-HEMPHILL
04/28/2016

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/8/2016

TO: Division of Anesthesia Analgesia and Addiction Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208042

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Sites Inspection

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials Early Phase Services, LLC	2455 N.E Loop 410, Suite 150 San Antonio, TX
Analytical		(b) (4)

Reference ID: 4320607

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/s/

SHILA S NKAH
03/08/2016