

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208042Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesia, Analgesia, and Addiction Products

NDA/BLA #s: 208042
Products: CASSIPA (buprenorphine and naloxone) (b) (4) film
SPONSOR: TEVA Pharmaceuticals
FROM: Judith A. Racoosin, MD, MPH
DATE: September 7, 2018

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

Since Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone) sublingual tablets were approved on October 8, 2002, we have become aware of data showing an increase in misuse and abuse of these products, as well as reports of children accidentally exposed to Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone). Reports from postmarketing surveillance reveal an upward trend in indices of extent of abuse of Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone) as noted in interviews of patients entering substance abuse treatment. Additionally, the reports show that there is an illegal trade in buprenorphine products which involves patients selling, bartering, or giving away their own prescribed medications to friends. The reports also show that prescribing practices by some physicians contribute to the availability of buprenorphine for abuse and misuse. Furthermore, a CDC report¹ published in January 2013 showed a disproportionate number of emergency department visits and hospitalizations due to pediatric accidental exposures to Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone). In 2009 buprenorphine products accounted for only 2.2% of retail opioid prescriptions, but Suboxone accounted for 9.5% of emergent hospitalizations for drug ingestion by children aged <6. We considered this information to be “new safety

¹ Emergency Department Visits and Hospitalizations for Buprenorphine Ingestion by Children — United States, 2010–2011. *Morbidity and Mortality Weekly Report* 2013; 16(3): 56.

information” as defined in the Food and Drug Administration Amendments Act of 2007 (FDAAA).

A REMS for Suboxone (buprenorphine/naloxone) film was approved in August 2010. A REMS for Suboxone (buprenorphine/naloxone) and Subutex (buprenorphine) tablets was approved in December 2011. The BTOD (Buprenorphine for the Treatment of Opioid Dependence) REMS was approved in February 2013 for generic oral transmucosal buprenorphine products. ZUBSOLV, a buprenorphine/naloxone sublingual tablet with a different dosing regimen than Suboxone, was approved on July 3, 2013, and joined the BTOD REMS on September 4, 2013. BUNAVAIL, a buprenorphine/naloxone buccal film was approved on June 6, 2014, as a member of the BTOD REMS.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for CASSIPA (buprenorphine and naloxone), a 505(b)(2) NDA, that is a buprenorphine and naloxone (b) (4) film to ensure the benefits of CASSIPA (buprenorphine and naloxone) outweigh the risks of accidental overdose, misuse, and abuse. In reaching this determination, we considered the following:

- A. CASSIPA (buprenorphine and naloxone) is indicated for the (b) (4) of opioid dependence. The estimated number of patients in the United States classified with opioid use disorder is 2.1 million persons aged 12 and over. Opioid use disorder encompasses heroin use disorder and pain reliever use disorder. This estimate is based the 2016 National Survey on Drug Use and Health.²
- B. Opioid dependence is a serious and life-threatening condition associated with morbidity and mortality due to overdose, blood-borne and sexually-transmitted diseases, and a variety of psychosocial consequences.
- C. CASSIPA (buprenorphine and naloxone) is effective in the (b) (4) of opioid dependence as measured by improvements in drug use behavior and retention in treatment.
- D. Treatment with CASSIPA (buprenorphine and naloxone) may continue indefinitely.
- E. CASSIPA (buprenorphine and naloxone) is associated with adverse events including abuse and accidental overdose leading to potentially lethal respiratory depression, hepatotoxicity, allergic reactions, and accidental pediatric exposures which are potentially lethal. Abuse and accidental overdose are common in the population, as

² <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>

are hepatic events attributable to blood-borne illnesses and use of other hepatotoxic substances.

F. CASSIPA (buprenorphine and naloxone) is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for CASSIPA (buprenorphine and naloxone). FDA has determined that CASSIPA (buprenorphine and naloxone) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of CASSIPA (buprenorphine and naloxone). FDA has determined that CASSIPA (buprenorphine and naloxone) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, CASSIPA (buprenorphine and naloxone).

The elements of the REMS include:

- A Medication Guide;
- Elements to assure safe use under 505-1(f)(3)(D) and (E) to ensure that each patient receives CASSIPA under safe use conditions and is subject to certain monitoring;
- An implementation system to ensure that patients receive CASSIPA under safe use conditions;
- And a timetable for submission of assessments of the REMS.

This REMS will use a waiver-granted shared system, specifically the BTOD (Buprenorphine for the Treatment of Opioid Dependence) REMS, for the elements to assure safe use, implementation system, and the REMS assessments.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SWATI A PATWARDHAN
09/07/2018

JUDITH A RACOOSIN
09/07/2018

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

| | |
|-------------------------------|---|
| Application Type | NDA |
| Application Number | 208042 |
| PDUFA Goal Date | September 8, 2018 |
| OSE RCM # | 2018-605 |
| Reviewer/Team Leader | Selena Ready, Pharm.D |
| Division Director | Cynthia LaCivita, Pharm.D |
| Review Completion Date | August 28, 2018 |
| Subject | Evaluation of Proposed REMS |
| Established Name | buprenorphine and naloxone |
| Trade Name | Cassipa |
| Name of Applicant | Teva Pharmaceuticals, USA |
| Therapeutic Class | Partial Opioid agonist-antagonist |
| Formulation(s) | 16 mg/ 4 mg sublingual film |
| Dosing Regimen | For maintenance only: 16 mg/4 mg as a single daily dose |

TABLE OF CONTENTS

| | | |
|-----|---|---|
| 1 | Introduction | 3 |
| 2 | Background | 3 |
| 2.1 | Product Information | 3 |
| 2.2 | Regulatory History..... | 4 |
| 3 | Materials Reviewed..... | 5 |
| 4 | Summary of Proposed REMS Submission and DRISK Comments..... | 5 |
| 4.1 | REMS Document | 6 |
| 4.2 | REMS Prescriber and Pharmacist Brochures | 6 |
| 4.3 | REMS Prescriber and Pharmacist Letters | 6 |
| 4.4 | REMS Appropriate Use Checklist..... | 6 |
| 4.5 | REMS Website Screenshots..... | 6 |
| 4.6 | REMS Supporting Document | 6 |
| 5 | Discussion and Conclusion..... | 7 |
| 6 | Recommendation..... | 7 |
| 7 | Attachment..... | 7 |

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Cassipa (buprenorphine and naloxone 16 mg/ 4 mg) sublingual (SL) film, new drug application (NDA) 208042, submitted by Teva Pharmaceuticals USA (Applicant) on March 27, 2018 and amended on April 18, 2018, July 19, 2018, August 16, 2018 and August 24, 2018. The proposed indication is for the maintenance treatment of opioid dependence and the product should be used as part of a complete treatment plan to include counseling and psychosocial support. This NDA was previously issued a Complete Response letter on September 30, 2016 and is under review in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

Since Cassipa is a buprenorphine-containing transmucosal product proposed for use in opioid dependence, if approved, it will join the shared system Buprenorphine-Containing Transmucosal products for Opioid Dependence (BTOD) REMS. The Applicant's proposed REMS includes a modified BTOD REMS to include their product, and prescribing information where appropriate. The Medication Guide (MG) will be evaluated in a separate review by the Office of Medical Policy, Division of Labeling Review.

2 Background

2.1 PRODUCT INFORMATION

Cassipa contains buprenorphine and naloxone 16 mg/ 4 mg as a SL film. Buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa opioid receptor. Naloxone is a potent antagonist at mu opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally. The proposed recommended dose is 16 mg/4 mg (1 SL film) daily for maintenance treatment of opioid dependence. It is to be initiated after treatment induction and stabilization of the patient and the patient has been titrated to a dose of 16 mg of buprenorphine using another marketed product.

Buprenorphine and naloxone SL film has been approved in the United States since 2010, marketed as Suboxone SL film (NDA 22410) supplied as 2 mg/0.5 mg and 8 mg/2 mg. Suboxone SL film is approved with the Suboxone (buprenorphine and naloxone) Sublingual Film and Tablets CIII and Subutex (buprenorphine) Sublingual Tablets CIII REMS (Suboxone/Subutex REMS). While Suboxone and Subutex were approved with a REMS for their respective products, the applicable generic versions were approved with a comparable, shared REMS, which was named the BTOD REMS. The BTOD REMS was developed by the Buprenorphine Products Manufacturing Group (BPMG), contains the same goals and elements as the Subutex/ Suboxone REMS, and was approved on February 22, 2013.

The BTOD REMS program is a waiver-granted shared system REMS, and includes all marketed buprenorphine-containing products approved for opioid dependence, except those manufactured

by Indivior Inc. The most recently approved BTOD REMS (last modified in May 2017) consists of a MG, elements to assure safe use (ETASU), a timetable for submission of assessments, and an implementation system. The safety concerns addressed by the BTOD REMS program are the potential for accidental overdose, misuse, and abuse.

The goals of the BTOD REMS program are to:

- Mitigate the risks of accidental overdose, misuse and abuse.
- Inform prescribers, pharmacists, and patients of the serious risks associated with buprenorphine containing products.

The objectives of the BTOD REMS program address the importance of: appropriate use of buprenorphine-containing products for the treatment of opioid dependence, adhering to the conditions of safe use and storage of the medication, the need for receiving the psychosocial support considered necessary for safe and effective treatment, and guarding against unintentional pediatric exposure.

The timetable for submission of assessments is annually with a due date of August (b) (4), beginning in 2014.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208042 relevant to this review:

October 29, 2014: NDA 208042 submission for maintenance treatment of opioid dependence received.

December 19, 2014: Refuse to file letter issued by the Agency.

November 30, 2015: Resubmission after refusal to file; the submission contained a REMS proposal with the BTOD REMS approved in February 2015.

September 2, 2016: The Agency provided comments to the Applicant regarding their proposed REMS.¹

September 30, 2016: The Agency issued a Complete Response letter to the Applicant.

March 8, 2018: The Applicant resubmitted NDA 208042 in response to the Complete Response letter dated September 30, 2016.

March 22, 2018: The Agency sent an IR for the Applicant to submit a REMS for the resubmission.

March 27, 2018: The Applicant submitted a proposed REMS.

¹ Hart, L. DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dehydrate 16 mg/4 mg sublingual film. September 2, 2016. DARRTS Reference ID 3981042.

April 18, 2018: The Applicant submitted an amended REMS.

June 29, 2018: The Agency provided comments to the Applicant regarding their proposed REMS submitted on April 18, 2018.²

July 19, 2018: The Applicant submitted an amended REMS proposal.

August 3, 2018: The Agency provided comments to the Applicant regarding their proposed REMS submitted on July 19, 2018.³

August 16, 2018: The Applicant submitted an amended REMS proposal.

August 23, 2018: The Agency sent an email to the Applicant regarding their proposed REMS submitted on August 16, 2018. *“You must resubmit the correct formatted version of the Prescriber Brochure and a Compiled REMS with the correct documents compiled. In your submission on August 21, 2018, you submitted the incorrect pdf formatted version of the Prescriber Brochure. If you compare page 6 of the formatted version of the Prescriber Brochure with Page 9 of the clean Word version of the Prescriber Brochure, you will note the difference. We’ve attached the documents for your reference.”*

August 24, 2018: The Applicant submitted amended PDFs of the proposed REMS Prescriber Brochure and the compiled documents for posting on the REMS@FDA website.

3 Materials Reviewed

- Teva Pharmaceuticals USA, REMS submission for buprenorphine naloxone sublingual film (NDA 209229), received on March 27, 2018 (ORIG-1; eCTD Sequence No. 0015)
 - Amendment received on April 18, 2018 (ORIG-1; eCTD Sequence No. 0017)
 - Amendment received on July 19, 2018 (ORIG-1; Sequence No. 0022)
 - Amendment received on August 16, 2018 (ORIG-1; Sequence No. 0024)
 - Amendment received on August 24, 2018 (ORIG-1; Sequence No. 0026)
- Draft Prescribing Information for Buprenorphine and Naloxone Sublingual Film, for sublingual use CIII (ORIG-1; eCTD Sequence No. 0014)
- BTOD REMS, approved on May 23, 2017.

4 Summary of Proposed REMS Submission and DRISK Comments

² Ready, S. DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dehydrate 16 mg/4 mg sublingual film. June 28, 2018. DARRTS Reference ID 4283486.

³ Ready, S. DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dehydrate 16 mg/4 mg sublingual film. August 2, 2018. DARRTS Reference ID 4301498.

The amended REMS proposal incorporates edits recommended by the Agency and includes a REMS Document, BTOD REMS Prescriber Brochure and Letter, BTOD REMS Pharmacist Brochure and Letter, BTOD REMS Appropriate Use Checklist, REMS Supporting Document, and BTOD REMS Website Screenshots that are revised to include their product.

4.1 REMS DOCUMENT

The Applicant submitted a proposed REMS Document which is the BTOD REMS Document approved on May 23, 2017 and provided on the REMS@FDA website.

Reviewer Comments: *This is acceptable to DRISK.*

4.2 REMS PRESCRIBER AND PHARMACIST BROCHURES

The proposed Brochures submitted by the Applicant included edits recommended by the Agency. The Applicant included the approved Trade Name in the list of products approved with the BTOD REMS provided in the Prescriber and Pharmacist Brochures. In addition, the Applicant included a revised table for “Corresponding doses of buprenorphine products that contain naloxone” and incorporated the Agency recommendations for adding the target dose for their product in the “Maintenance with Buprenorphine-Containing Products” Section in the Prescriber Brochure.

Reviewer Comments: *This is acceptable to DRISK.*

4.3 REMS PRESCRIBER AND PHARMACIST LETTERS

The Applicant submitted the BTOD REMS Prescriber and Pharmacists Letters and did not propose any edits.

Reviewer Comment: *This is acceptable to DRISK.*

4.4 REMS APPROPRIATE USE CHECKLIST

The Applicant incorporated the recommended edits provided by the Agency and included the product with the proposed target dose into the Appropriate Use Checklist under the “Maintenance” section of the under “Assessed appropriateness of dosage.”

Reviewer Comment: *This is acceptable to DRISK.*

4.5 REMS WEBSITE SCREENSHOTS

The website screenshots include the approved Trade Name and generic name in the list of products included under the BTOD REMS.

Reviewer Comment: *This is acceptable to DRISK.*

4.6 REMS SUPPORTING DOCUMENT

The Applicant submitted the REMS Supporting Document for the BTOD REMS and included Announcement Letters to be sent to the Prescribers and Pharmacists that informs of their product

being added to the BTOD REMS. These were added to the end of the REMS Supporting Document and they were also submitted separately for review.

Reviewer Comments: *This is acceptable to DRISK. The Announcement Letters, to be sent if the product is approved, is comparable to the letters approved for Bunavail and Zubsolv, when those Applications joined the BTOD REMS, and are included in the BTOD REMS Supporting Document.*

5 Discussion and Conclusion

Cassipa is a buprenorphine-containing transmucosal product for opioid dependence, and the Agency has determined a REMS is necessary to mitigate the risks of accidental overdose, misuse, and abuse for these products. If approved, Cassipa will join the shared system BTOD REMS, which was approved in February 2013 and last modified in May 2017. Because the NDA is for a higher dosage strength (16 mg buprenorphine/ 4 mg naloxone) than the NDAs currently approved in the BTOD REMS, the Applicant's proposed REMS includes a modified BTOD REMS to include Cassipa, and prescribing information where appropriate. Changes to the BTOD REMS materials include adding Cassipa to list of products covered in the BTOD REMS and updating the materials to reflect the new dosage strength available for maintenance treatment of opioid dependence. Cassipa will be added to the BTOD REMS appended materials and BTOD REMS Supporting Document. The MG will be evaluated in a separate review by the Division of Labeling Review.

DRISK agrees with the Applicant's proposed REMS. If the NDA is approved, the action will prompt a class-wide BTOD REMS modification. If a BTOD REMS modification is approved between the date of this review and action being taken on this application, this REMS review will no longer be applicable and the Applicant's proposed REMS should be considered deficient. If Cassipa is approved, the list of approved products will be updated on FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) website.

6 Recommendation

DRISK recommends approval of the proposed REMS for Cassipa (buprenorphine 16mg and naloxone 4 mg SL film), received on March 27, 2018, as amended and appended to this review.

7 Attachment

REMS Document and Materials

32 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SELENA D READY
08/28/2018

CYNTHIA L LACIVITA
08/28/2018

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

| | |
|-------------------------------|---|
| Application Type | NDA |
| Application Number | 208042 |
| PDUFA Goal Date | August 2, 2018 |
| OSE RCM # | 2018-605 |
| Reviewer/Team Leader | Selena Ready, Pharm.D |
| Division Director | Cynthia LaCivita, Pharm.D |
| Review Completion Date | June 27, 2018 |
| Subject | Evaluation of Proposed REMS |
| Established Name | buprenorphine and naloxone |
| Trade Name | Under Review by DMEPA |
| Name of Applicant | Teva Pharmaceuticals, USA |
| Therapeutic Class | Partial Opioid agonist-antagonist |
| Formulation(s) | 16 mg/ 4 mg sublingual film |
| Dosing Regimen | For maintenance only: 16 mg/4 mg as a single daily dose |

TABLE OF CONTENTS

| | | |
|-----|--|---|
| 1 | Introduction | 3 |
| 2 | Background | 3 |
| 2.1 | Product Information | 3 |
| 2.2 | Regulatory History | 4 |
| 3 | Materials Reviewed | 5 |
| 4 | Summary of Proposed REMS Submission and DRISK Comments | 5 |
| 4.1 | REMS Document | 5 |
| 4.2 | REMS Prescriber and Pharmacist Brochures | 5 |
| 4.3 | REMS Prescriber and Pharmacist Letters | 6 |
| 4.4 | REMS Appropriate Use Checklist | 6 |
| 4.5 | REMS Website Screenshots | 6 |
| 4.6 | REMS Supporting Document | 6 |
| 5 | Discussion and Conclusion | 6 |
| 6 | Comments for the Sponsor | 7 |
| | ATTACHMENTS | 8 |

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for buprenorphine and naloxone 16 mg/ 4 mg sublingual (SL) film, new drug application (NDA) 208042, submitted by Teva Pharmaceuticals USA (Applicant) on March 27, 2018 and amended on April 18, 2018 and July 19, 2018. The proposed indication is for the maintenance treatment of opioid dependence and the product should be used as part of a complete treatment plan to include counseling and psychosocial support. This NDA was previously issued a Complete Response letter on September 30, 2016 and is under review for a second cycle in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

During the first review cycle, DRISK completed an evaluation of the REMS proposal and provided comments to the Applicant on September 2, 2016.¹ Thus, this review provides further comments to the Applicant regarding their proposed REMS. Since this product is a buprenorphine-containing transmucosal product proposed for use in opioid dependence, if approved, it will join the shared system Buprenorphine-Containing Transmucosal products for Opioid Dependence (BTOD) REMS. The Applicant's proposed REMS includes a modified BTOD REMS to include their product, and prescribing information where appropriate. The Medication Guide (MG) will be evaluated in a separate review by the Office of Medical Policy, Division of Labeling Review.

2 Background

2.1 PRODUCT INFORMATION

Buprenorphine and naloxone 16 mg/ 4 mg SL film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally. The proposed recommended dose is 16 mg/4 mg (1 SL film) daily for maintenance treatment of opioid dependence. It is to be initiated after treatment induction and stabilization of the patient and the patient has been titrated to a dose of 16 mg using another marketed product.

Buprenorphine and naloxone SL film has been approved in the United States since 2010, marketed as Suboxone SL film (NDA 22410) supplied as 2 mg/0.5 mg and 8 mg/2 mg. Suboxone SL film is approved with the Suboxone (buprenorphine and naloxone) Sublingual Film and Tablets CIII and Subutex (buprenorphine) Sublingual Tablets CIII REMS (Suboxone/Subutex REMS). While Suboxone and Subutex were approved with a REMS for their respective products, the applicable generic versions were approved with a comparable, shared REMS, which was named the BTOD REMS. The BTOD REMS was developed by the Buprenorphine Products Manufacturing Group (BPMG), contains the same goals and elements as the Subutex/ Suboxone REMS, and was approved on February 22, 2013.

¹ Hart, L. DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dehydrate 16 mg/4 mg sublingual film. September 2, 2016. DARRTS Reference ID 3981042.

The BTOD REMS program is a waiver-granted shared system REMS, and includes all marketed buprenorphine-containing products approved for opioid dependence, except those manufactured by Indivior Inc. The most recently approved BTOD REMS (last modified in May 2017) consists of a MG, elements to assure safe use (ETASU), a timetable for submission of assessments, and an implementation system. The safety concerns addressed by the BTOD REMS program are the potential for accidental overdose, misuse, and abuse.

The goals of the BTOD REMS program are to:

- Mitigate the risks of accidental overdose, misuse and abuse.
- Inform prescribers, pharmacists, and patients of the serious risks associated buprenorphine containing products.

The objectives of the BTOD REMS program address the importance of: appropriate use of buprenorphine-containing products for the treatment of opioid dependence, adhering to the conditions of safe use and storage of the medication, the need for receiving the psychosocial support considered necessary for safe and effective treatment, and guarding against unintentional pediatric exposure.

The timetable for submission of assessments is annually with a due date of August ^(b)₍₄₎st, beginning in ^(b)₍₄₎.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208042 relevant to this review:

October 29, 2014: NDA 208042 submission for maintenance treatment of opioid dependence received.

December 19, 2014: Refuse to file letter issued by the Agency.

November 30, 2015: Resubmission after refusal to file; the submission contained a REMS proposal with the BTOD REMS approved in February 2015.

September 2, 2016: The Agency provided comments to the Applicant regarding their proposed REMS.

September 30, 2016: The Agency issued a Complete Response letter to the Applicant.

March 8, 2018: The Applicant resubmitted NDA 208042 in response to the Complete Response letter dated September 30, 2016.

March 22, 2018: The Agency sent an IR for the Applicant to submit a REMS for the resubmission.

March 27, 2018: The Applicant submitted a proposed REMS.

April 18, 2018: The Applicant submitted an amended REMS.

June 29, 2018: The Agency provided comments to the Applicant regarding their proposed REMS submitted on April 18, 2018.

July 19, 2018: The Applicant submitted an amended REMS proposal. These materials are the subject of this review.

3 Materials Reviewed

- Teva Pharmaceuticals USA, REMS submission for buprenorphine naloxone sublingual film (NDA 209229), received on March 27, 2018 (ORIG-1; eCTD Sequence No. 0015)
 - Amendment received on April 18, 2018 (ORIG-1; eCTD Sequence No. 0017)
 - Amendment received on July 19, 2018 (ORIG-1; Sequence No. 0022)
- Draft Prescribing Information for Buprenorphine and Naloxone Sublingual Film, for sublingual use CIII (ORIG-1; eCTD Sequence No. 0014)
- Hart, L. DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dehydrate 16 mg/4 mg sublingual film. September 2, 2016.
- BTOD REMS, approved on May 23, 2017.

4 Summary of Proposed REMS Submission and DRISK Comments

The Applicant amended their proposed REMS to include most of the edits recommended by the Agency on June 29, 2018. The amended REMS proposal includes a REMS Document, BTOD REMS Prescriber Brochure and Letter, BTOD REMS Pharmacist Brochure and Letter, BTOD REMS Appropriate Use Checklist, and BTOD REMS Website Screenshots that are revised to include their product.

4.1 REMS DOCUMENT

The Applicant resubmitted a proposed REMS Document in the Structured Product Labeling (SPL) format, which is not the BTOD REMS Document approved on May 23, 2017 and provided on the REMS@FDA website.

Reviewer Comments: *The proposed REMS Document is not the correct REMS Document for the BTOD REMS. The correct BTOD REMS Document was approved on May 23, 2017 and is provided on the REMS@FDA website. The Applicant must resubmit the approved version of the BTOD REMS Document to their application.*

4.2 REMS PRESCRIBER AND PHARMACIST BROCHURES

The proposed Brochures submitted by the Applicant included edits recommended by the Agency on June 29, 2018. The Applicant included the place holder for the approved Trade Name in the list of products approved with the BTOD REMS provided in the Prescriber and Pharmacist Brochures. In addition, the Applicant included a revised table for “Corresponding doses of buprenorphine products that contain naloxone” and incorporate the Agency recommendations for adding the target dose for their product in the “Maintenance with Buprenorphine-Containing Products” Section in the Prescriber Brochure.

Reviewer Comments: *This is acceptable to DRISK. However, the approved proprietary name that is listed in the labeling must be inserted in the final formatted versions for approval.*

4.3 REMS PRESCRIBER AND PHARMACIST LETTERS

The Applicant did not propose any edits to the BTOD REMS Prescriber or Pharmacists Letters.

Reviewer Comment: *This is acceptable to DRISK.*

4.4 REMS APPROPRIATE USE CHECKLIST

The Applicant incorporated the recommended edits provided by the Agency on June 29, 2018 and included the product with the proposed target dose into the Appropriate Use Checklist under the “Maintenance” section of the under “Assessed appropriateness of dosage.”

Reviewer Comment: *This is acceptable to DRISK. However, the approved proprietary name that is listed in the labeling must be inserted in the final formatted versions for approval.*

4.5 REMS WEBSITE SCREENSHOTS

The website screenshots include the place holder for the approved Trade Name and generic name in the list of products included under the BTOD REMS.

Reviewer Comment: *This is acceptable to DRISK. However, the approved proprietary name that is listed in the labeling must be inserted in the final formatted versions for approval.*

4.6 REMS SUPPORTING DOCUMENT

The Applicant incorporated the recommended edits provided by the Agency on June 29, 2018 and included their product redlined in the list of approved products. Also, the Applicant submitted the Announcement Letters to be sent to the Prescribers and Pharmacists that informs of their product being added to the BTOD REMS. These were added to the end of the REMS Supporting Document and they were also submitted separately for review.

Reviewer Comments: *The Announcement Letters, to be sent if the product is approved, is comparable to the letters approved for Bunavail and Zubsolv, when those Applications joined the BTOD REMS, and will be included in the BTOD REMS Supporting Document. There were edits to the Announcement Letters that must be made for clarity and the approved proprietary name that is listed in the labeling must be inserted in the final formatted versions for approval. Refer to the attached redlined documents.*

5 Discussion and Conclusion

This product is a buprenorphine-containing transmucosal product proposed for use in opioid dependence and, if approved, it will join the shared system BTOD REMS. The Applicant’s proposed REMS includes a modified BTOD REMS to include their product, and prescribing information where appropriate. Overall, DRISK agrees with the global changes to the proposed REMS submission in that the Applicant incorporated their product. However, the Applicant must submit the BTOD REMS Document approved on May 23, 2017 and make further changes to the REMS materials to align with the final labeling. The MG will be evaluated in a separate review by the Division of Labeling Review.

6 Comments for the Sponsor

General Comments:

- Note redlined revisions on the attached MS Word versions of the materials and make the same changes to the pdf formatted versions.
- Ensure that all content is consistent across all the REMS materials and website.
- Insert the approved proprietary name that will be listed in the labeling in the final Word and formatted versions of the REMS materials and website screenshots.

REMS Document

You submitted the wrong version of the BTOD REMS Document a second time. Refer to the attachment which provides the BTOD REM Document approved on May 23, 2017, which is listed on the REMS@FDA. Submit this approved version of the BTOD REMS Document to your application.

Prescriber and Pharmacist Brochures

We note that you included the recommended edits. However, you must insert the approved proprietary name that is listed in the labeling in the final formatted versions and resubmit.

REMS Prescriber and Pharmacist Letters

These materials are acceptable.

Appropriate Use Checklist

We note that you included the recommended edits and this material is acceptable. However, you must insert the approved proprietary name that is listed in the labeling in the final formatted versions and resubmit.

REMS Website Screenshots

You must insert the approved proprietary name that is listed in the labeling in the final formatted versions and resubmit.

REMS Supporting Document

We note that you included the recommended edits to the BTOD REMS Supporting Document to include your product, and the separate submission of the Announcement Letters, to be sent if approved. We have included a couple of edits to the Announcement Letters. Refer to the attached redlined documents.

Resubmission Instructions:

Submit the REMS materials to your application by **Monday, August 20, 2018**. **Any questions on the materials should be communicated immediately upon opening of the business day.** All content in the materials must align with the revised Prescribing Information.

The next submission should include Redlined, Clean MS Word, and final formatted versions of the following documents:

- ***REMS Document***

- **REMS Supporting Document (do not include in the compiled PDF document)**
- **REMS Appropriate Use Checklist**
- **REMS Prescriber and Pharmacist Brochures**
- **REMS Prescriber and Pharmacist Letters**
- **REMS Announcement Letters (do not include in the compiled PDF document)**
- **REMS Website Screenshots**
- **A compiled pdf document which includes the REMS Document, all REMS materials, and website screenshots (note these screenshots are homepage shots only).** This would not include the REMS Supporting Document, Announcement Letters, or MS Word version of the Website Content.

ATTACHMENTS

1. BTOD REMS Document, Approved May 23, 2017
2. Agency Redlined Announcement Prescriber Letter
3. Agency Redlined Announcement Pharmacist Letter

14 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SELENA D READY
08/02/2018

CYNTHIA L LACIVITA
08/02/2018

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

| | |
|-------------------------------|---|
| Application Type | NDA |
| Application Number | 208042 |
| PDUFA Goal Date | September 8, 2018 |
| OSE RCM # | 2018-605 |
| Reviewer/Team Leader | Selena Ready, Pharm.D |
| Division Director | Cynthia LaCivita, Pharm.D |
| Review Completion Date | June 27, 2018 |
| Subject | Evaluation of Proposed REMS |
| Established Name | buprenorphine and naloxone |
| Trade Name | Under Review by DMEPA |
| Name of Applicant | Teva Pharmaceuticals, USA |
| Therapeutic Class | Partial Opioid agonist-antagonist |
| Formulation(s) | 16 mg/ 4 mg sublingual film |
| Dosing Regimen | For maintenance only: 16 mg/4 mg as a single daily dose |

TABLE OF CONTENTS

| | | |
|-----|--|---|
| 1 | Introduction | 3 |
| 2 | Background | 3 |
| 2.1 | Product Information | 3 |
| 2.2 | Regulatory History | 4 |
| 3 | Materials Reviewed | 4 |
| 4 | Summary of Proposed REMS Submission and DRISK Comments | 5 |
| 4.1 | REMS Document | 5 |
| 4.2 | REMS Prescriber and Pharmacist Letters..... | 5 |
| 4.3 | REMS Prescriber and Pharmacist Brochures | 5 |
| 4.4 | REMS Appropriate Use Checklist | 6 |
| 4.5 | REMS Website Screenshots | 6 |
| 4.6 | REMS Supporting Document..... | 7 |
| 5 | Discussion and Conclusion | 7 |
| 6 | Comments for the Sponsor | 7 |

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates the proposed risk evaluation and mitigation strategy (REMS) for buprenorphine and naloxone 16 mg/ 4 mg sublingual (SL) film, new drug application (NDA) 208042, submitted by Teva Pharmaceuticals USA (Applicant) on March 27, 2018 and amended on April 18, 2018. The proposed indication is for the maintenance treatment of opioid dependence and the product should be used as part of a complete treatment plan to include counseling and psychosocial support. This NDA was previously issued a Complete Response letter on September 30, 2016 and is under review for a second cycle in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP).

During the first review cycle, DRISK completed an evaluation of the REMS proposal and provided comments to the Applicant on September 2, 2016.¹ Thus, this review provides further comments to the Applicant regarding their proposed REMS. Since this product is a buprenorphine-containing transmucosal product proposed for use in opioid dependence, if approved, it will join the shared system Buprenorphine-Containing Transmucosal products for Opioid Dependence (BTOD) REMS. The Applicant's proposed REMS includes a modified BTOD REMS to include their product, and prescribing information where appropriate. The Medication Guide (MG) will be evaluated in a separate review by the Office of Medical Policy, Division of Labeling Review.

2 Background

2.1 PRODUCT INFORMATION

Buprenorphine and naloxone 16 mg/ 4 mg SL film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally. The proposed recommended dose is 16 mg/4 mg (1 SL film) daily for maintenance treatment of opioid dependence. It is to be initiated after treatment induction and stabilization of the patient and the patient has been tritrated to a dose of 16 mg using another marketed product.

Buprenorphine and naloxone SL film has been approved in the United States since 2010, marketed as Suboxone SL film (NDA 22410) supplied as 2 mg/0.5 mg and 8 mg/2 mg. Suboxone SL film is approved with the Suboxone (buprenorphine and naloxone) Sublingual Film and Tablets CIII and Subutex (buprenorphine) Sublingual Tablets CIII REMS (Suboxone/Subutex REMS). While Suboxone and Subutex were approved with a REMS for their respective products, the applicable generic versions were approved with a comparable, shared REMS, which was named the BTOD REMS. The BTOD REMS was developed by the Buprenorphine Products Manufacturing Group (BPMG), contains the same goals and elements as the Subutex/ Suboxone REMS, and was approved on February 22, 2013.

¹ Hart, L. DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dehydrate 16 mg/4 mg sublingual film. September 2, 2016. DARRTS Reference ID 3981042.

The BTOD REMS program is a waiver-granted shared system REMS, and includes all marketed buprenorphine-containing products approved for opioid dependence, except those manufactured by Indivior Inc. The most recently approved BTOD REMS (last modified in May 2017) consists of a Medication Guide, elements to assure safe use (ETASU), a timetable for submission of assessments, and an implementation system.

The safety concerns addressed by the BTOD REMS program are the potential for accidental overdose, misuse, and abuse.

The goals of the BTOD REMS program are to:

- Mitigate the risks of accidental overdose, misuse and abuse.
- Inform prescribers, pharmacists, and patients of the serious risks associated buprenorphine containing products.

The objectives of the BTOD REMS program address the importance of: appropriate use of buprenorphine-containing products for the treatment of opioid dependence, adhering to the conditions of safe use and storage of the medication, the need for receiving the psychosocial support considered necessary for safe and effective treatment, and guarding against unintentional pediatric exposure.

The timetable for submission of assessments is annually with a due date of August (b) (4)st, beginning in (b) (4).

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208042 relevant to this review:

October 29, 2014: NDA 208042 submission for maintenance treatment of opioid dependence received.

December 19, 2014: Refuse to file letter issued by the Agency.

November 30, 2015: Resubmission after refusal to file; the submission contained a REMS proposal with the BTOD REMS approved in February 2015.

September 2, 2016: DRISK reviewed the REMS proposal and provided comments to the Applicant.

September 30, 2016: The Agency issued a Complete Response letter to the Applicant.

March 8, 2018: The Applicant resubmitted NDA 208042 in response to the Complete Response letter dated September 30, 2016.

March 22, 2018: The Agency sent an IR for the Applicant to submit a REMS for the resubmission.

March 27, 2018: The Applicant submitted a proposed REMS.

April 18, 2018: The Applicant submitted an amended REMS proposal and these materials are the subject of this review.

3 Materials Reviewed

- Teva Pharmaceuticals USA, REMS submission for buprenorphine naloxone sublingual film (NDA 209229), received on March 27, 2018 (ORIG-1; eCTD Sequence No. 0015)

- Amendment received on April 18, 2018 (ORIG-1; eCTD Sequence No. 0017)
- Draft Prescribing Information for Buprenorphine and Naloxone Sublingual Film, for sublingual use CIII (ORIG-1; eCTD Sequence No. 0014)
- Hart, L. DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dehydrate 16 mg/4 mg sublingual film. September 2, 2016.
- BTOD REMS, approved on May 23, 2017.

4 Summary of Proposed REMS Submission and DRISK Comments

The Applicant's proposed REMS included a REMS document, BTOD REMS Prescriber Brochure and Letter, BTOD REMS Pharmacist Brochure and Letter, BTOD REMS Appropriate Use Checklist, and BTOD REMS Website Screenshots that are revised to include their product.

4.1 REMS DOCUMENT

The Applicant submitted a proposed BTOD REMS Document in the Structured Product Labeling (SPL) format.

Reviewer Comments: *The proposed REMS Document is not the correct REMS Document for the BTOD REMS. The correct BTOD REMS Document was approved on May 23, 2017 and is provided on the REMS@FDA website. The Applicant must resubmit the approved version of the BTOD REMS Document to their application.*

4.2 REMS PRESCRIBER AND PHARMACIST BROCHURES

The materials submitted by the Applicant includes the place holder for the approved Trade Name in the list of products approved with the BTOD REMS provided in the Prescriber and Pharmacist Brochures. In addition, the Applicant included a revised table for "Corresponding doses of buprenorphine products that contain naloxone." The Applicant added a column to the table and provided their product in the column. See Figure 1 below. The Applicant also added a footnote to the table in the Pharmacist's Brochure regarding the route of administration.

In addition, the Applicant did not incorporate the Agency recommendations for adding the target dose for their product in the "Maintenance with Buprenorphine-Containing Products" Section in the Prescriber Brochure.

Reviewer Comments: *DRISK determined that the proposed table (Figure 1) is not acceptable because the proposed indication lists the product's route of administration for sublingual administration and [REDACTED] (b) (4). The Applicant must remove the term "[REDACTED] (b) (4)", as well as remove the footnote that occurs in the Pharmacist Brochure.*

The Applicant must include their product in the "Maintenance with Buprenorphine-Containing Products" Section in the Prescriber Brochure. Refer to the attached redlined document.

Figure 1: Table 1 Excerpt from the Applicant’s proposed REMS Prescriber Brochure

| | | Table 1 Corresponding doses of buprenorphine products that contain naloxone | | | | |
|--------------------------|---|--|---|--|---|--|
| Product Name | Buprenorphine sublingual tablets (Subutex®) | Buprenorphine/Naloxone sublingual tablets (Suboxone®) | Buprenorphine/Naloxone sublingual films (Suboxone®) | Buprenorphine/Naloxone sublingual tablets (Zubsolv®) | Buprenorphine/Naloxone buccal films (Bunavail®) | Buprenorphine/Naloxone sublingual films (Trade Name) |
| Dose Strengths Available | | | | 0.7 mg buprenorphine/ 0.18 mg naloxone | | |
| | 2 mg buprenorphine | 2 mg buprenorphine/ 0.5 mg naloxone | 2 mg buprenorphine/ 0.5 mg naloxone | 1.4 mg buprenorphine/ 0.36 mg naloxone | | |
| | | | 4 mg buprenorphine/ 1 mg naloxone | 2.9 mg buprenorphine/ 0.71 mg naloxone | 2.1 mg buprenorphine/ 0.3 mg naloxone | |
| | 8 mg buprenorphine | 8 mg buprenorphine/ 2 mg naloxone | 8 mg buprenorphine/ 2 mg naloxone | 5.7 mg buprenorphine/ 1.4 mg naloxone | 4.2 mg buprenorphine/ 0.7 mg naloxone | |
| | | | 12 mg buprenorphine/ 3 mg naloxone | 8.6 mg buprenorphine/ 2.1 mg naloxone | 6.3 mg buprenorphine/ 1 mg naloxone | |
| Route of Administration | Sublingual | Sublingual | Sublingual Buccal | Sublingual | Buccal | Sublingual (b) (4) |

4.3 REMS PRESCRIBER AND PHARMACIST LETTERS

The Applicant did not propose any edits to the BTOD REMS Prescriber or Pharmacists Letters.

Reviewer Comment: *This is acceptable to DRISK.*

4.4 REMS APPROPRIATE USE CHECKLIST

The Applicant incorporated the recommended edits provided by the Agency on September 2, 2016 and included the product with the proposed target dose into the Appropriate Use Checklist under the “Maintenance” section of the under “Assessed appropriateness of dosage.” However, the Applicant did not position the product in the next bullet following the Suboxone SL Film as the Agency recommended in their comments on September 2, 2016.

Reviewer Comment: *DRISK determined that the language is acceptable. However, we recommend that the product be positioned in the bullet following the Suboxone SL tablet and film. Refer to the attached redlined document.*

4.5 REMS WEBSITE SCREENSHOTS

The Applicant incorporated the comments provided by the Agency on September 2, 2016.

Reviewer Comment: *This is acceptable to DRISK.*

4.6 REMS SUPPORTING DOCUMENT

The Applicant submitted a REMS Supporting Document that did not include their product redlined in the list of approved products. Also, the Applicant added “Announcement Letters” to be sent to the Prescribers and Pharmacists that informs of their product being added to the BTOD REMS. These were added to the end of the REMS Supporting Document and not submitted separately.

Reviewer Comments: *The product must be incorporated in the REMS Supporting Document with the next submission. The “Announcement Letters,” to be sent if the product is approved, is comparable to the letters approved for Bunavail and Zubsolv, when those Applications joined the BTOD REMS. However, the Applicant must submit these letters as a separate material for review, and the proposed table with “Corresponding doses of buprenorphine product that contain naloxone” that is included in the letter must align with the table in the Prescriber and Pharmacist Brochures. Refer to the attached redlined document.*

5 Discussion and Conclusion

This product is a buprenorphine-containing transmucosal product proposed for use in opioid dependence and, if approved, it will join the shared system BTOD REMS. The Applicant’s proposed REMS includes a modified BTOD REMS to include their product, and prescribing information where appropriate. Overall, DRISK agrees with the global changes to the proposed REMS submission in that the Applicant incorporated their product. However, the Applicant must submit the currently approved BTOD REMS Document and make further changes to the REMS materials to align with the proposed labeling. The MG will be evaluated in a separate review by the Division of Labeling Review.

6 Comments for the Sponsor

General Comments:

- Note redlined revisions on the attached MS Word versions of the materials and make the same changes to the pdf formatted versions.
- Ensure that all content is consistent across all the REMS materials and website.

REMS Document

Submit the approved version of the BTOD REMS Document to your application. The correct BTOD REMS Document was approved on May 23, 2017 and is provided on the REMS@FDA website.

Prescriber and Pharmacist Brochures

*The proposed table “Corresponding doses of buprenorphine products that contain naloxone” is not acceptable because the proposed indication is for sublingual administration and (b) (4). The Applicant must remove the term (b) (4), as well as remove the footnote that occurs in the Pharmacist Brochure. **The table must be consistent in both Brochures.** In addition, the Applicant must include their product in the “Maintenance with Buprenorphine-Containing Products” Section in the Prescriber Brochure. Refer to the attached redlined document for edits.*

REMS Prescriber and Pharmacist Letters

We note that you did not edit the BTOD REMS Prescriber and Pharmacist Letters. These materials are acceptable.

Appropriate Use Checklist

We recommend that the product be positioned in the bullet following the Suboxone SL tablet and film. Refer to the attached redlined document for edits.

REMS Website Screenshots

We note that you edited this material to include your product. This material is acceptable.

REMS Supporting Document

The product must be incorporated in the REMS Supporting Document with the next submission. We note the addition of Announcement Letters in the Supporting Document. Submit the "Announcement Letters" as a separate material for review, and correct the proposed table with "Corresponding doses of buprenorphine product that contain naloxone." The information must align with the table in the Prescriber and Pharmacist Brochures. Refer to the attached redlined document.

Resubmission Instructions:

Submit the REMS materials to your application by **Friday, July 20, 2018**. **Any questions on the materials should be communicated immediately upon opening of the business day.** All content in the materials **must align with the revised Prescribing Information.**

The next submission should include Redlined, Clean MS Word, and final formatted versions of the following documents:

- ***REMS Document***
- ***REMS Supporting Document (do not include in the compiled PDF document)***
- ***REMS Appropriate Use Checklist***
- ***REMS Prescriber and Pharmacist Brochures***
- ***REMS Prescriber and Pharmacist Letters***
- ***REMS Announcement Letters (do not include in the compiled PDF document)***
- ***REMS Website Screenshots***
- ***A compiled pdf document which includes the REMS Document, all REMS materials, and website screenshots (note these screenshots are homepage shots only).*** This would not include the REMS Supporting Document, Announcement Letters, or MS Word version of the Website Content.

ATTACHMENTS

1. REMS Appropriate Use Checklist
2. REMS Prescriber Brochure
3. REMS Supporting Document (email only)

17 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SELENA D READY
06/27/2018

CYNTHIA L LACIVITA
06/28/2018

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

| | |
|-------------------------------|---|
| Application Type | New Drug Application (NDA) |
| Application Number | 208042 |
| PDUFA Goal Date | September 30, 2016 |
| OSE RCM # | 2015-2675 |
| Reviewer Name(s) | Leah Hart, Pharm.D. |
| DRISK Team Leader | Division of Risk Management (DRISK) |
| Division Director | Kim Lehrfeld, Pharm.D. |
| Review Completion Date | Cynthia LaCivita, Pharm.D. |
| (Date DARRTED) | September 02, 2016 |
| Subject | DRISK Review for buprenorphine hydrochloride (HCL)/naloxone HCL dihydrate, 16 mg/4 mg sublingual film |
| Established Name | Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg |
| (Proposed) Trade Name | buprenorphine and naloxone, 16 mg/4 mg sublingual film |
| Applicant | Teva Pharmaceuticals USA |
| Therapeutic Class | Opioid partial agonist-antagonist |
| Formulation(s) | Sublingual Film |
| Dosing Regimen | 16 mg/4 mg sublingually daily as directed |

Table of Contents

| | |
|---|----|
| EXECUTIVE SUMMARY | 4 |
| 1 Introduction..... | 4 |
| 2 Background | 4 |
| 2.1 Product Information | 4 |
| 2.2 Regulatory History..... | 4 |
| 3 Therapeutic Context and Treatment Options | 5 |
| 3.1 Description of the Medical Condition | 5 |
| 3.2 Description of Current Treatment Options | 5 |
| 4 Benefit Assessment | 6 |
| 5 Risk Assessment & Safe-Use Conditions | 6 |
| 5.1 Serious Risks | 7 |
| 5.2 Safe Use Conditions | 7 |
| 6 Expected Postmarket Use..... | 8 |
| 7 Evaluating the need for a REMS..... | 9 |
| 8 Risk Management Activities Proposed by the Applicant..... | 9 |
| 8.1 Review of Applicant’s Proposed REMS | 9 |
| 8.1.1 REMS Goals..... | 9 |
| 8.1.2 REMS Requirements..... | 9 |
| 8.1.3 REMS Materials | 10 |
| 8.1.4 REMS Assessment Plan | 12 |
| 8.2 Other Proposed Risk Management Activities | 16 |
| 9 Conclusion & Recommendations..... | 16 |
| 10 Comments for the Applicant..... | 16 |
| 11 Materials Reviewed..... | 18 |

12 Appendices 18

1

2 EXECUTIVE SUMMARY

3 This review by the Division of Risk Management (DRISK) documents the recommendations on the
4 proposed risk evaluation and mitigation strategy (REMS) for Buprenorphine and Naloxone
5 Sublingual Film, 16 mg/4 mg (NDA 208042), originally submitted on November 30, 2015 after a
6 refusal to file by Teva Pharmaceuticals USA (Teva), and amended on August 22, 2016 that is
7 currently under review.

8 1 Introduction

9 The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) requested the Division of Risk
10 Management's (DRISK) evaluation of buprenorphine hydrochloride (HCL)/naloxone HCL dihydrate,
11 16 mg/4 mg sublingual film, NDA 208042, to assess the need for a Risk Evaluation and Mitigation
12 Strategy (REMS). Buprenorphine hydrochloride (HCL)/naloxone HCL dihydrate, 16 mg/4 mg
13 sublingual film will be hereafter referred to as Buprenorphine and Naloxone Sublingual (SL) Film.
14 This review documents DRISK's evaluation of the proposed REMS for Buprenorphine and Naloxone
15 SL Film, submitted by Teva Pharmaceutical USA (Teva) on August 22, 2016. If approved this product
16 will be included in the shared REMS, the Buprenorphine-containing Transmucosal products for
17 Opioid Dependence (BTOD) REMS.

18 2 Background

19 2.1 PRODUCT INFORMATION

20 Buprenorphine, a semi-synthetic opioid, is a partial mu-opioid receptor agonist and a kappa-opioid
21 receptor antagonist. The transmucosal sublingual formulations are indicated for the treatment of
22 opioid dependence. In combination with naloxone, it is indicated for treatment of opioid
23 dependence¹. The proposed indication for this application is the maintenance treatment of opioid
24 dependence.

25 2.2 REGULATORY HISTORY

26 The following is a summary of the regulatory history for NDA 208042 relevant to this review:

- 27 • October 29, 2014: NDA 208042 submission for maintenance treatment of opioid
28 dependence received
- 29 • December 19, 2014: Refuse to file
- 30 • November 30, 2015: Resubmission after refusal to file, this submission contained a
31 proposed REMS based on the February 12, 2015 approved BTOD REMS.

¹ Bunavail and Suboxone sublingual tablets (including generic formulations) are approved for the maintenance treatment of opioid dependence

- 32 • July 7, 2016: BTOD REMS Modification approved which included revision of materials to
33 emphasize the risk messages and reduce the burden on the healthcare delivery system.
- 34 • August 22, 2016: Applicant submitted an amendment containing a proposed REMS based on
35 the July 7, 2016 (revised July 27, 2016) with the product incorporated. This proposed REMS
36 is the subject of this review.

37 **3 Therapeutic Context and Treatment Options**

38 **3.1 DESCRIPTION OF THE MEDICAL CONDITION**

39 Opioid dependence is defined by International Statistical Classification of Diseases and Related
40 Health Problems (ICD)-10 as the “presence of three or more [of the following: a strong desire or
41 sense of compulsion to take opioids; difficulties in controlling opioid use; a physiological withdrawal
42 state; tolerance; progressive neglect of alternative pleasures or interest because of opioid use;
43 persisting with opioid use despite clear evidence of overtly harmful consequences] present
44 simultaneously at any one time in the preceding year”²

45 Of the 21.5 million Americans 12 or older that had substance dependence in 2014, 1.9 million
46 involved prescription pain relievers and 586,000 involved heroin.³ Drug overdose is the leading
47 cause of accidental death in the US, with 47,055 lethal drug overdoses in 2014. Opioid addiction is
48 driving this epidemic, with 18,893 overdose deaths related to prescription pain relievers, and 10,574
49 overdose deaths related to heroin in 2014⁴.

50 **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

51 Treatment of opioid dependence combines pharmacological and psychosocial interventions
52 designed to reduce or cease opioid use. The pharmacological options include use of an opioid
53 agonist (i.e. methadone), a partial opioid agonist (i.e. buprenorphine), or an alpha-2 adrenergic
54 agonist (i.e. clonidine). Agonist maintenance treatment, either with an opioid agonist or opioid
55 partial agonist, maintains a stable level of opioid effect avoiding both intoxication and withdrawal.

² World Health Organization (WHO). 1992. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization.

³ Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. Rockville, MD: Substance Abuse and Mental Health Services Administration.

⁴ Center for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, Mortality File. (2015). Number and Age-Adjusted Rates of Drug-poisoning Deaths Involving Opioid Analgesics and Heroin: United States, 2000–2014. Atlanta, GA: Center for Disease Control and Prevention.

56 Agonist maintenance treatment is indicated for all patients who are opioid dependent and are able
57 to give informed consent, and for whom there are no specific contraindications⁵.

58 **4 Benefit Assessment**

59 The NDA for Buprenorphine and Naloxone SL Film is a 505(b)(2) application referencing the Agency's
60 previous finding of efficacy for the Reference Listed Drug (RLD) Suboxone sublingual film (NDA
61 22410). In the NDA for Suboxone sublingual film, no new efficacy data was submitted and the
62 efficacy relied on the Agency's previous finding of efficacy based on the approved NDAs for Subutex
63 sublingual tablet (NDA 20732) and Suboxone sublingual tablet (NDA 20733). In accordance with
64 Section 505(b)(2) of the Food Drug and Cosmetic act, the Applicant conducted a bioequivalence
65 study that established the bioequivalence of Buprenorphine and Naloxone Sublingual Film with
66 Suboxone sublingual film. The Applicant's submission indicated that Buprenorphine and Naloxone SL
67 Film was found to be bioequivalent with two of Suboxone 8 mg/ 2mg sublingual films. In addition,
68 the Applicant also conducted two additional studies to evaluate the effects of pre-treatment
69 beverage temperature and pre-treatment beverage pH on the relative bioavailability of the product.
70 The clinical pharmacology review⁶ concluded that Buprenorphine and Naloxone SL Film "exhibited
71 equivalent systemic exposure (C_{max}, AUC_{last}, and AUC_{inf}) to buprenorphine and naloxone in
72 comparison to the listed drug, Suboxone sublingual film 2 x 8/2 mg."

73 **5 Risk Assessment & Safe-Use Conditions**

74 Three Phase I studies were conducted to provide, in part, the basis for the safety assessments for
75 Buprenorphine and Naloxone SL Film. Additional safety data is provided by a review of the literature
76 and from the labeling for the reference listed drug (Suboxone sublingual film).

77 Based on the Applicant's submission, the adverse events (AEs) reported most frequently (in $\geq 5\%$ of
78 subjects) in the combined phase 1 studies were nausea, vomiting, oral paresthesia, abdominal pain,
79 headache, dizziness, somnolence and euphoric mood. These adverse events are consistent with the
80 known safety profile of Suboxone and/or the known pharmacological effects of opioids. Based on
81 the Applicant's report, no severe events were reported during any of the studies and the majority of
82 all adverse events were generally mild in severity with the exception of nausea and vomiting, which
83 were generally mild to moderate in severity. The Applicant attributed the adverse event of euphoric
84 mood, and increased incidence of oral paresthesia, nausea and vomiting to the study population
85 given that these were Phase I studies in healthy subjects rather than the indicated population with
86 no titration to the recommended target maintenance dose.

⁵ WHO 2009 Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence.

⁶ Qiu, W., Clinical Pharmacology Review for Buprenorphine and naloxone sublingual film. August 17, 2016.

87 The literature review of adverse events conducted by the Applicant did not reveal any new safety
88 findings. No clinically significant changes in laboratory data, vital signs, or ECG findings were noted
89 in the combined Phase I studies. Overall, the clinical studies supporting approval of the application
90 demonstrated a similar safety profile to that expected for buprenorphine-containing products and
91 did not indicate that there are unexpected adverse events or unusual rates of adverse events
92 associated with Buprenorphine and Naloxone SL Film.

93 **5.1 SERIOUS RISKS**

94 Reckitt Benckiser Pharmaceutical's (RBP), Subutex sublingual tablets and Suboxone sublingual
95 tablets were approved by the Agency on October 8, 2002, for the treatment of opioid dependence.
96 These products were approved with Risk Minimization Action Plans (RiskMAPs).

97 In 2009, the Agency became aware of data showing an increase in misuse and abuse of Subutex and
98 Suboxone, as well as reports of children aged six and younger accidentally exposed to these
99 products. Based on the safety concerns, it was determined by the Agency that a REMS would be
100 necessary to mitigate the risks of accidental overdose, misuse and abuse⁷.

101 RBP's Suboxone sublingual film was approved on August 30, 2010 for use in the maintenance
102 treatment of opioid dependence. As part of the approval of Suboxone sublingual film, the Agency
103 required a REMS to ensure the benefits of the drug outweigh the risks. On December 22, 2011, a
104 similar REMS with the same components was approved for Subutex sublingual tablets and Suboxone
105 sublingual tablets.

106 While Subutex and Suboxone were approved with a REMS for their respective products, the
107 applicable generic versions were approved with a comparable, shared REMS, the Buprenorphine-
108 containing Transmucosal products for Opioid Dependence (BTOD) REMS. The BTOD REMS was
109 developed by the Buprenorphine Products Manufacturers Group (BPMG) and contains the same
110 goals and elements as the Subutex and Suboxone REMS programs and was approved along with the
111 applications for several generic versions of these products on February 22, 2013. Two NDA Sponsors
112 have joined the BTOD with the approval of their applications; Zubsolv sublingual tablet (NDA
113 204242) was approved on July 3, 2013 and Bunavail buccal film (NDA 205637) was approved on June
114 6, 2014.

115 **5.2 SAFE USE CONDITIONS**

116 A risk management plan had been in place for Suboxone and Subutex sublingual tablets since their
117 approval in October 2002. Between 2002 and 2009 new safety information regarding an increase in
118 misuse and abuse of Subutex and Suboxone and reports of pediatric accidental exposure was
119 identified and in 2009 it was determined that a REMS was necessary to ensure the benefits

⁷ Bunting, J. DRISK response to Office of Regulatory Policy's Consult Request regarding the Citizen Petition for Suboxone, dated February 21, 2013.

120 outweighed the risks of (1) exposure to Suboxone sublingual film in persons for whom it was not
121 prescribed, including accidental exposure in children and (2) risks of abuse and misuse. RBP received
122 a CR letter⁸ for Suboxone film (NDA 22410) notifying the Sponsor that based on the Agency's
123 understanding of the risks of buprenorphine, it was determined that the REMS must include a
124 Medication Guide (due to the serious and significant public health concern and necessary for
125 patients' safe and effective use of the product), elements to assure safe use under 505-1(f)(3)(D)
126 and 505-1(f)(3)(E) (each patient using the drug be subject to certain clinical monitoring under
127 section 505(f)(3)(E) of the FDCA to ensure that 1) each patient is receiving the psychosocial support
128 necessary for safe use and effective use of Suboxone film, 2) each patient adheres to the conditions
129 of safe use explained to him/her, and 3) each patient is using Suboxone film appropriately and
130 making adequate progress towards treatment goals), an implementation system, and a timetable
131 for the submission of assessments of the REMS.

132 The approval of generic oral transmucosal buprenorphine prompted the approval of a waiver-
133 granted shared system with a comparable REMS to that of the innovator (Suboxone and Subutex
134 sublingual tablets) called the Buprenorphine-containing Transmucosal products for Opioid
135 Dependence (BTOD) REMS was approved in February 2013.

136 The most recently approved BTOD REMS (last approved July 7, 2016 and revised July 27, 2016)
137 consists of a Medication Guide, elements to assure safe use, and implementation system.

138 The goals of this REMS are to:

- 139 • Mitigate the risks of accidental overdose, misuse, and abuse
- 140 • Inform prescribers, pharmacists and patients of the serious risks associated with the use of
141 buprenorphine-containing products

142
143 Additionally, the objectives of the REMS address the importance of appropriate use of
144 buprenorphine products for the treatment of opioid dependence; the importance of adhering to the
145 conditions of safe use; the importance of safe storage of medication; the need for receiving the
146 psychosocial support considered necessary for safe and effective treatment; and the importance of
147 guarding against unintentional pediatric exposure.

148 **6 Expected Postmarket Use**

149 This buprenorphine and naloxone product will be approved for (b) (4)
150 (b) (4) opioid dependence and will be subject

⁸ Food and Drug Administration, Complete Response letter to Reckitt Benckiser Pharmaceuticals for Suboxone (buprenorphine/naloxone) sublingual film, NDA 22410, dated August 21, 2009.

151 to the same buprenorphine class-wide REMS. The expected postmarket use will be no different than
152 that of the already approved drugs in the class.

153 **7 Evaluating the need for a REMS**

154 Past regulatory actions did require REMS to mitigate the risk of accidental overdose, misuse, and
155 abuse and the decision to require a REMS is consistent with these prior actions. Buprenorphine and
156 naloxone sublingual film is a buprenorphine-containing transmucosal product for opioid
157 dependence, and the Agency has determined a REMS is necessary to mitigate the risks of accidental
158 overdose, misuse, and abuse for these products.

159 **8 Risk Management Activities Proposed by the Applicant**

160 **8.1 REVIEW OF APPLICANT'S PROPOSED REMS**

161 The Applicant submitted the July 7, 2016 (revised on July 27, 2016) approved version of the BTOD
162 REMS document, appended materials and Supporting Document with revisions to include
163 Buprenorphine and Naloxone Sublingual Film.
164

165 **8.1.1 REMS Goals**

166 The goals of the Buprenorphine-containing Transmucosal products for Opioid
167 Dependence (BTOD) REMS are to:

- 168 • Mitigate the risks of accidental overdose, misuse, and abuse
- 169 • Inform prescribers, pharmacists, and patients of the serious risks
170 associated with buprenorphine-containing products

171 **8.1.2 REMS Requirements**

172 **8.1.2.1 Medication Guide**

173 As one element of a REMS, FDA may require the development of a Medication Guide as provided for
174 under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Buprenorphine and
175 Naloxone Sublingual Films pose a serious and significant public health concern requiring the
176 distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and
177 effective use of Buprenorphine and Naloxone Sublingual Films. FDA has determined that
178 Buprenorphine and Naloxone Sublingual Film is a product for which patient labeling could help
179 prevent serious adverse effects and that has serious risks (relative to benefits) of which patients
180 should be made aware because information concerning the risks could affect patients' decisions to
181 use, or continue to use, Buprenorphine and Naloxone Sublingual Films.

182 Under 21 CFR 208, the Applicant is responsible for ensuring that the Medication Guide is available
183 for distribution to patients who are dispensed Buprenorphine and Naloxone Sublingual Films.

184 **8.1.2.2 Elements to Assure Safe Use**

185 In addition, we have determined that a Medication Guide and a communication plan are not
186 sufficient to mitigate the serious risks. The REMS must include elements to manage these risks,
187 including the following:

- 188 • The drug is dispensed to patients with evidence or other documentation of safe-use
189 conditions [section 505-1(f)(3)(D)]
- 190 • Each patient using the drug is subject to certain monitoring [section 505-1(f)(3)(E)]

191 **8.1.2.3 Implementation System**

192 The REMS must include an implementation system to monitor and evaluate the implementation of
193 the elements to assure safe use (outlined above) that require the drug be dispensed to patients with
194 documentation of safe use conditions.

195 **8.1.3 REMS Materials**

196 **8.1.3.1 REMS Document**

197 *Reviewer comment: The Applicant did not propose any edits to the REMS document.*

198 **8.1.3.2 Dear Prescriber Letter**

199 *Reviewer comment: The Applicant did not propose any edits to the Dear Prescriber Letter*

200 **8.1.3.3 Dear Pharmacist Letter**

201 *Reviewer comment: The Applicant did not propose any edits to the Dear Pharmacist Letter*

202 **8.1.3.4 Appropriate Use Checklist**

203 The Applicant added their product to the Appropriate Use Checklist in the **Assessed appropriateness**
204 **of dosage** section to read:

205 Buprenorphine combined with naloxone is recommended for maintenance:

- 206 • Buprenorphine and naloxone SL tablet (b) (4) and film (SUBOXONE®): doses ranging from
207 12 mg to 16 mg of buprenorphine are recommended for maintenance
- 208 • (b) (4)
- 209 • Buprenorphine and naloxone SL tablet (ZUBSOLV®): a target dose of 11.4 mg buprenorphine is
210 recommended for maintenance
- 211 • Buprenorphine and naloxone buccal film (BUNAVAIL™): a target dose of 8.4 mg of buprenorphine is
212 recommended for maintenance

213

214 *Reviewer comment: The Applicant's proposed Appropriate Use Checklist revisions are not*
215 *acceptable as no maintenance dose recommendation was included in the product line. The product*
216 *should be inserted to read (see attached redlined Appropriate Use Checklist):*

217

- 218 • Buprenorphine and naloxone SL tablet (b) (4) and film (SUBOXONE®): doses ranging from
219 12 mg to 16 mg of buprenorphine are recommended for maintenance
- 220 • Buprenorphine and naloxone sublingual film (b) (4): a target dose 16
221 mg of buprenorphine is recommended for maintenance

- 222 • Buprenorphine and naloxone SL tablet (ZUBSOLV®): a target dose of 11.4 mg buprenorphine is
223 recommended for maintenance
- 224 • Buprenorphine and naloxone buccal film (BUNAVAIL™): a target dose of 8.4 mg of buprenorphine is
225 recommended for maintenance

226 **8.1.3.5 Prescriber Brochure, “Office-Based Buprenorphine Therapy for Opioid**
227 **Dependence: Important Information for Prescribers” and Pharmacist**
228 **Brochure, “Office-Based Buprenorphine Therapy for Opioid Dependence:**
229 **Important Information for Pharmacists”**

230 The Applicant added their product to the Prescriber and Pharmacist Brochures in the list of products
231 covered in the BTOD REMS, and the Corresponding Doses table.

232 *Reviewer comment: DRISK disagrees with the placement of Buprenorphine and Naloxone SL Film in*
233 *both the list of products covered in the BTOD REMS and the Corresponding Doses table. See attached*
234 *redlined Prescriber and Pharmacist Brochures for the preferred inclusion of the product.*

235 *In addition, in the Prescriber Brochure section **Maintenance with buprenorphine-containing***
236 ***products**, Buprenorphine and Naloxone must be incorporated. The section currently reads:*

237 The recommended target dose is 16 mg buprenorphine/4 mg naloxone per day for Suboxone
238 sublingual tablets and sublingual film, including generic equivalents, and is 11.4 mg
239 buprenorphine/2.8 mg naloxone per day for Zubsolv sublingual tablet, and 8.4 mg
240 buprenorphine/1.4 mg naloxone per day for Bunavail buccal film. Clinical studies have shown
241 that these are clinically effective doses. Although lower doses may be effective in some patients,
242 for most patients, this dose should alleviate withdrawal symptoms and block or attenuate the
243 effects of other opioid agonists for at least 24 hours.

244 The upper limit of the recommended dose is 24 mg per day for Suboxone sublingual tablets and
245 sublingual film, including generic equivalents, 17.1 mg per day for Zubsolv, and 12.6 mg per day
246 for Bunavail.

247

248 *The revised section with Buprenorphine and Naloxone SL Film incorporated should read (see*
249 *attached Agency redlined Prescriber Brochure):*

250 The recommended target dose is:

- 251 • 16 mg buprenorphine/4 mg naloxone per day for:

252  (b) (4)

- 255 • 11.4 mg buprenorphine/2.8 mg naloxone per day for  (b) (4)
256  ZUBSOLV®

257 • 8.4 mg buprenorphine/1.4 mg naloxone per day (b) (4) BUNAVAIL®).

258 Clinical studies have shown that these are clinically effective doses. Although lower doses may be

259 effective in some patients, for most patients, this dose should alleviate withdrawal symptoms and

260 block or attenuate the effects of other opioid agonists for at least 24 hours.

261 The upper limit of the recommended dose is:

- 262 • 24 mg (b) (4) per day for (b) (4):
- 263 ○ (b) (4)
- 264 ○ (b) (4)
- 265 • 17.1 mg (b) (4) per day for (b) (4)
- 266 ZUBSOLV®)
- 267 • 12.6 mg per day for (b) (4) BUNAVAIL®)

268 **8.1.3.6 BTOD REMS Website**

269 The Applicant did not add Buprenorphine and Naloxone SL Film to the BTOD REMS Website as a

270 drug product subject to the Buprenorphine-containing Transmucosal products for Opioid

271 Dependence (BTOD) REMS.

272 *Reviewer comment: Buprenorphine and Naloxone Sublingual Film should be incorporated into the*

273 *most recently approved BTOD REMS Website as a drug product subject to the BTOD REMS (see*

274 *attached redlined BTOD REMS Website).*

275 **8.1.3.7 REMS Supporting Document**

276 The Applicant submitted a REMS Supporting Document with the November 30, 2015 submission

277 that included insertion of their product as well as a BTOD announcement letter. The amended

278 submission on August 22, 2016 did not contain a REMS Supporting Document.

279 *Reviewer comment: Buprenorphine and Naloxone Sublingual Film should be incorporated into the*

280 *most recent BTOD REMS Supporting Document and be included with the next submission.*

281 **8.1.4 REMS Assessment Plan**

282 The BTOD submission of assessments occurs annually with a due date of August 30th. The following

283 table details the REMS Assessment Plan for the BTOD REMS.

| Assessment Elements | BTOD Sponsors Shared Commitments |
|---------------------|----------------------------------|
| (b) (4) | |

284

285 **8.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES**

286 The Applicant did not propose any additional risk management activities.

287 **9 Conclusion & Recommendations**

288 A REMS for Buprenorphine and Naloxone Sublingual Film is necessary to ensure the benefits
289 outweigh this risks of serious adverse outcomes (e.g., accidental overdose, misuse, and abuse).
290 DRISK agrees with the Applicant’s proposal to join the BTOD REMS and include Buprenorphine and
291 Naloxone Sublingual Film within the BTOD REMS document, BTOD REMS appended materials and
292 BTOD REMS Supporting Document. The proposed REMS is currently under review.

293 **10 Comments for the Applicant**

294 1. *The proposed addition to the **Appropriate Use Checklist** is not acceptable as no*
295 *maintenance dose recommendation was included in the product line. The*
296 *product should be inserted to read (see attached redlined **Appropriate Use***
297 *Checklist):*

- 298 • Buprenorphine and naloxone SL tablet (b) (4) and film (SUBOXONE®): doses ranging
299 from 12 mg to 16 mg of buprenorphine are recommended for maintenance
- 300 • Buprenorphine and naloxone sublingual film ((b) (4)): a target dose
301 16 mg of buprenorphine is recommended for maintenance
- 302 • Buprenorphine and naloxone SL tablet (ZUBSOLV®): a target dose of 11.4 mg buprenorphine is
303 recommended for maintenance
- 304 • Buprenorphine and naloxone buccal film (BUNAVAIL™): a target dose of 8.4 mg of buprenorphine
305 is recommended for maintenance

307 2. *The placement of Buprenorphine and Naloxone SL Film in both the list of*
308 *products covered in the BTOD REMS and the Corresponding Doses table in the*
309 ***Prescriber and Pharmacist Brochures** is not acceptable. See attached redlined*
310 *Prescriber and Pharmacist Brochures for the preferred inclusion of the product.*

311 3. *In addition, in the **Prescriber Brochure** section **Maintenance with***
312 ***buprenorphine-containing products**, Buprenorphine and Naloxone must be*
313 *incorporated. The section currently reads:*

314 [Redacted text] (b) (4)

315 [Redacted text] (b) (4)

316 (b) (4)
317 (b) (4) Clinical studies have shown
318 that these are clinically effective doses. Although lower doses may be effective in some patients,
319 for most patients, this dose should alleviate withdrawal symptoms and block or attenuate the
320 effects of other opioid agonists for at least 24 hours.

321 The upper limit of the recommended dose is 24 mg per day for Suboxone sublingual tablets and
322 sublingual film, including generic equivalents, 17.1 mg per day for Zubsolv, and 12.6 mg per day
323 for Bunavail.

324 *The revised section with Buprenorphine and Naloxone SL Film incorporated should read (see*
325 *attached Agency redlined Prescriber Brochure):*

326 The recommended target dose is:

- 327 • 16 mg buprenorphine/4 mg naloxone per day for:
328 (b) (4)
329
330
- 331 • 11.4 mg buprenorphine/2.8 mg naloxone per day for (b) (4)
332 ZUBSOLV®)
- 333 • 8.4 mg buprenorphine/1.4 mg naloxone per day for (b) (4) BUNAVAIL®).

334 Clinical studies have shown that these are clinically effective doses. Although lower doses may
335 be effective in some patients, for most patients, this dose should alleviate withdrawal symptoms
336 and block or attenuate the effects of other opioid agonists for at least 24 hours.

337 The upper limit of the recommended dose is:

- 338 • 24 mg (b) (4) per day for (b) (4):
339 (b) (4)
340
 - 341 • 17.1 mg (b) (4) per day for (b) (4)
342 ZUBSOLV®)
 - 343 • 12.6 mg per day for (b) (4) BUNAVAIL®)
- 344 4. *Buprenorphine and Naloxone Sublingual Film should be incorporated into the most*
345 *recently approved BTOD REMS Website as a drug product subject to the BTOD REMS*
346 *(see attached redlined BTOD REMS Website).*
 - 347 5. *A REMS Supporting Document was included with the November 30, 2015 submission*
348 *however the amended submission on August 22, 2016 did not contain a REMS*

349 *Supporting Document. Buprenorphine and Naloxone Sublingual Film should be*
350 *incorporated into the most recent BTOD REMS Supporting Document and be*
351 *included with the next submission.*

- 352 6. Final submissions to the FDA should include:
- 353 a. Submit in MS Word format any documents that have been revised with
 - 354 track changes.
 - 355 b. Submit your proposed REMS and other materials in the final, formatted PDF
 - 356 format. The entire REMS document and appended materials should be in a
 - 357 single PDF document.
 - 358 c. Submit the REMS Supporting Document as a separate document, in MS
 - 359 Word track changes format if revised and PDF if no changes were necessary.
 - 360 d. The submitted version of Website screenshots should be in final format, as
 - 361 this will be posted on the FDA approved REMS website (REMS@FDA) if this
 - 362 application is approved.
 - 363

364 **11 Materials Reviewed**

365 The following is a list of materials informing this review:

- 366 1. Teva Pharmaceuticals USA. Risk Evaluation and Mitigation Strategy for buprenorphine
- 367 hydrochloride (HCL)/naloxone HCL dihydrate, 16 mg/4 mg sublingual film, dated November 30,
- 368 2015.
- 369 2. Teva Pharmaceuticals USA. Proposed Prescribing Information for buprenorphine hydrochloride
- 370 (HCL)/naloxone HCL dihydrate, 16 mg/4 mg sublingual film, dated March 14, 2016.
- 371 3. Teva Pharmaceuticals USA. Clinical Overview for buprenorphine hydrochloride (HCL)/naloxone
- 372 HCL dihydrate, 16 mg/4 mg sublingual film, dated November 20, 2015.
- 373 4. Teva Pharmaceuticals USA. Summary of Clinical Safety for buprenorphine hydrochloride
- 374 (HCL)/naloxone HCL dihydrate, 16 mg/4 mg sublingual film, dated November 20, 2015.
- 375 5. Qiu,W., Division of Anesthesia Analgesia and Addictive Products. Clinical Pharmacology Review
- 376 for Buprenorphine and naloxone sublingual film, NDA 208042, dated August 17, 2016.

377 **12 Appendices**

- 378 1. Appropriate Use Checklist- REDLINED
- 379
- 380 2. BTOD REMS Website- REDLINED

- 381 **3.** Prescriber Brochure, “Office-Based Buprenorphine Therapy for Opioid Dependence: Important
382 Information for Prescribers”
- 383 **4.** Pharmacist Brochure, “Office-Based Buprenorphine Therapy for Opioid Dependence: Important
384 Information for Pharmacists”

36 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH M HART-BANKS
09/02/2016

CYNTHIA L LACIVITA
09/02/2016
Concur