

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208042Orig1s000**

**CLINICAL REVIEW(S)**



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

**Summary Review for Regulatory Action**

<b>Date</b>	September 30, 2016
<b>From</b>	Rigoberto Roca, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA No.</b>	208042
<b>Applicant Name</b>	Teva Pharmaceuticals
<b>Date of Submission</b>	November 30, 2015
<b>PDUFA Goal Date</b>	September 30, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Buprenorphine and naloxone sublingual film
<b>Dosage Forms / Strength</b>	16 mg/ 4 mg buprenorphine/naloxone sublingual film
<b>Proposed Indication</b>	Maintenance treatment of opioid dependence
<b>Action</b>	Complete Response

<b>Material Reviewed/Consulted: OND Action Package, including</b>	
CDTL Review	Celia Winchell, MD
Pharmacology Toxicology Review	Elizabeth Bolan, PhD; Dan Mellon, PhD
Clinical Pharmacology Review	Wei Qiu, PhD ; Yun Xu, PhD
OPQ	Ciby Abraham, PhD; Erika Englund, PhD; Donna Christner, PhD; Xiaobin Shen, PhD; Julia C. Pinto, PhD; Pei-I Chu, PhD; Ubrani Venkataram, PhD; Eric Adeeku, PhD; Rebecca Dombrowski, PhD; Steven Kinsley, PhD
Biopharmaceutics Review	Vidula Kolhatkar, PhD; Kelly Kitchens, PhD
Project Management Staff	Spiros Nicols, RPh; Matthew Sullivan, MS
DPMH	Leyla Sahin, MD; Lynne Yao, MD
DMEPA	James Schlick, RPh, MBA; Vicky Borders-Hemphill, PharmD
DRISK	L Hart, PharmD; K Lehrfeld, PharmD; Cynthia LaCivita, PharmD
CSS	A Trachtenberg, MD, MPH; J Randall-Thompson, PhD; Michael Klein, PhD
OSIS/DNDBE	Shila Nkah

CDTL = Cross-Discipline Team Leader  
 CSS = Controlled Substance Staff  
 DMEPA = Division of Medication Error Prevention and Analysis  
 DNDBE = Division of New Drug Bioequivalence Evaluation  
 DPMH = Division of Pediatric and Maternal Health

DRISK = Division of Risk Management  
 OND = Office of New Drugs  
 OPQ = Office of Pharmaceutical Quality  
 OSIS = Office of Study Integrity and Surveillance

## 1. Introduction

Teva Pharmaceuticals (the Applicant), has submitted a new drug application (NDA) for a buprenorphine/naloxone sublingual film. This submission is a 505 (b)(2) submission, utilizing Suboxone film as the reference product (NDA 22410). The Applicant proposes a single dosage unit that delivers 16 mg of buprenorphine and 4 mg of naloxone for maintenance treatment of opioid dependence. The recommended dose of Suboxone film for most patients is 16 mg of buprenorphine, once daily, delivered as two films that contain 8 mg of buprenorphine and 2 mg of naloxone each. The Applicant contends that, since there is currently no single-dose unit approved in the United States that delivers that dose of buprenorphine/naloxone, this product will improve dosing convenience and patient compliance.

The Applicant submitted the results of a bioequivalence study that compared their product to Suboxone (2 units of the Suboxone 8 mg buprenorphine/2 mg naloxone film). The Applicant also submitted the results of pharmacokinetic studies that evaluate the results of beverage temperature and beverage acidity.

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

## 2. Background

### Buprenorphine

Buprenorphine is a partial agonist at the  $\mu$ -opiate receptor. Buprenorphine was initially approved in 1981 as a parenteral formulation for the treatment of pain (Buprenex, NDA 18401). Since 1981, there have been eight NDAs containing buprenorphine approved:

- Sublingual tablet formulations intended for the treatment of opioid dependence
  - Subutex (buprenorphine), NDA 20732
  - Suboxone (buprenorphine/naloxone), NDA 20733
  - Zubsolv (buprenorphine/naloxone), NDA 204242
- Sublingual film formulation intended for the treatment of opioid dependence
  - Suboxone (buprenorphine/naloxone) film, NDA 22410
- Buccal film formulation intended for maintenance treatment of opioid dependence
  - Bunavail (buprenorphine) film, NDA 207932
- Implant
  - Probuphine (buprenorphine) NDA 204442
- Buccal film formulation intended for maintenance treatment of pain
  - Belbucca (buprenorphine/naloxone) film, NDA 205637
- Extended-release transdermal film formulation intended for the treatment of pain
  - Butrans (buprenorphine), NDA 21306

As noted in Dr. Winchell's review, buprenorphine was developed as a treatment for opioid dependence because of its pharmacological properties. Buprenorphine's activity at the  $\mu$ -

receptor was expected to relieve the patient's urge to use illicit opioids, and its long duration of action would allow a patient to achieve a steady state without the highs and lows associated with illicit opioids. Further, its partial agonist property was expected to result in a "ceiling" effect at moderate doses with respect to its euphorogenic effects. Lastly, at sufficiently high doses, buprenorphine blocks full agonists from achieving their full effects, which, in buprenorphine-maintained patients, would result in decreased use of these substances.

### Naloxone

Naloxone is a  $\mu$ -receptor antagonist, which, when used parenterally, produces opioid withdrawal signs and symptoms in subjects who are dependent on full opioid agonists. The incorporation of naloxone into Bunavail's formulation is not for the purposes of treating the opioid addiction, but rather, to provide an additional element of deterrence for intravenous misuse. As noted in Dr. Winchell's review, the naloxone is expected to be clinically inactive when the product is used as intended.

### Pre-submission Regulatory History

The major interactions between the Division and the Applicant prior to the submission of the NDA are well-summarized in Dr. Winchell's review. Significant recommendations conveyed to the Applicant in 2013 included the type of stability data, pharmacology-toxicology data that would be required, as well as the need to evaluate the effect of temperature and acidity on the bioavailability of their product.

The Applicant initially submitted their application on October 29, 2014, but the application was not filed due to the absence of several components. The Applicant subsequently resubmitted their application on November 30, 2015.

## **3. Chemistry, Manufacturing, and Controls (CMC)**

The following description of the product is reproduced from the OPQ reviews:

### *Drug Substance*

The drug substance, Buprenorphine HCl, USP is manufactured by Teva Czech Industries s.r.o. (TCI) and is referenced in DMF# 16419. Buprenorphine HCl is a white or almost white crystalline powder. Only one crystal form is found. The retest period for Buprenorphine HCl is (b) (4) months, when stored at (b) (4) °C.

The drug substance, Naloxone HCl Dihydrate, USP is manufactured by (b) (4) and is referenced in DMF# (b) (4). Naloxone HCl Dihydrate is a white crystalline powder. Only one crystal form is found. The retest period is (b) (4) months, when stored at (b) (4) °C.

### *Drug Product*

Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg is used for sublingual (b) (4) use. The test product is designed to be an immediate release dosage form and releases the two drug compounds within (b) (4) minutes. The unit dimension of the film is 22.3 mm x 25.4 mm, thickness: ~ 15  $\mu$ m, and weight: 93 mg. The films are

packaged individually in child resistant and (b) (4) pouches, consisting from (b) (4). Based on the stability data provided, an expiry of 24-months will be granted using the storage statement "Store at (b) (4); excursions permitted between 15° and 30°C (59° and 86°F). (b) (4)".

The application was found acceptable from a drug substance, drug product, microbiology, and biopharmaceutics perspective.

The drug product manufacturer, LTS Lohmann Therapy Systems site located in NJ (FEI 1000121692) was not ready for inspection and a withhold recommendation was provided by the home district (NWJ-DO). Without the manufacturing site ready for inspection, the process group had deficiencies about the manufacturing process of the Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg.

#### Outstanding or Unresolved Issues

Due to the fact that the drug product manufacturer site was not ready for inspection, the review team recommended a Complete Response for the application. I concur with the review team that this application cannot be approved at this time.

In addition, the review team identified the following issues that need to be addressed by the Applicant in the next review cycle:

1. The Applicant stated in their application that (1) the (b) (4) are considered high risk factors to product content uniformity, (2) critical process parameters such as (b) (4) will affect product assay results, and (3) acceptable (b) (4) will be evaluated and established during process scale-up and process validation. Therefore, the Applicant will need to provide the commercial (b) (4) equipment information, the critical process parameters for (b) (4) the commercial manufacturing process.
2. The Applicant will need to confirm that they will continue to perform the (b) (4) for the commercial batches. In addition, the Applicant proposed to conduct the content uniformity test in the drug product specification; therefore, the Applicant will need to provide justification that the sampling plan and acceptance criteria for the content uniformity test provides statistical assurance that batches of drug product will meet appropriate specifications and statistical quality control criteria.
3. The Applicant has selected (b) (4) film as a (b) (4) during the manufacturing of buprenorphine and naloxone sublingual film. The Applicant will need to provide information on the composition, physical attributes acceptance specification and a safety statement for (b) (4).
4. Revision of the butylated hydroxyanisole (BHA) acceptance limit.

## 5. Nonclinical Pharmacology/Toxicology

The Applicant did not submit any new nonclinical data for review. The review team concluded that the excipients in this formulation can be found in higher amounts in products approved for chronic use and do not pose any toxicologic concerns. All impurities/degradants in the drug substances and drug product are controlled at acceptable levels. There are no unique nonclinical issues with this product as compared to other sublingual formulations of its individual components, buprenorphine and naloxone.

The review team did evaluate the label for consistency with the Pregnancy and Lactation Labeling Rule (PLLR). The team made wording recommendations for purposes of updating the label.

### *Outstanding or Unresolved Issues*

I concur with Drs. Bolan and Mellon that there are no pharmacology/toxicology issues that would preclude approval of this application.

## 6. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted the results of a comparative bioavailability study, Study 3007599; an effect of temperature study, Study 4001650; and effect of pH study, Study 4001651. The final to-be-marketed formulation was used in all these PK Studies.

The design and results of these studies are well-described in Dr. Qui's review. The key clinical pharmacology findings were summarized as follows by Dr. Qiu (reproduced from her review):

1. Teva buprenorphine/naloxone sublingual film 1 x 16/4 mg exhibited equivalent systemic exposure (C<sub>max</sub>, AUC<sub>last</sub>, and AUC<sub>inf</sub>) to buprenorphine and naloxone in comparison to the listed drug, Suboxone sublingual film 2 x 8/2 mg.
2. Effect of Pretreatment with Cold Water: the systemic exposures (C<sub>max</sub>, AUC<sub>last</sub>, and AUC<sub>inf</sub>) of buprenorphine and naloxone following pretreatment with cold water was similar to that following pretreatment with a room temperature water.
3. Effect of Pretreatment with Hot Water: the systemic exposures of buprenorphine and naloxone following pretreatment with hot water was similar to that following pretreatment with a room temperature water except buprenorphine C<sub>max</sub> was increased by 15%.
4. Effect of Pretreatment with Low pH Beverage (Sprite): buprenorphine C<sub>max</sub> and AUC values were decreased by 14-15% and naloxone C<sub>max</sub> and AUC values were decreased by 30-36% following drinking Sprite.
5. Effect of Pretreatment with High pH Beverage (solution of ½ teaspoon of sodium bicarbonate): buprenorphine C<sub>max</sub> and AUC values were decreased by 14-16%. Naloxone C<sub>max</sub> and AUC<sub>last</sub> were increased by 142% and 89-92%, respectively following drinking solution of ½ teaspoon of sodium bicarbonate. The Sponsor proposes to instruct patients to avoid high pH beverages prior to dosing.

### *QT Assessment*

As noted in Dr. Winchell's review the Applicant did not conduct any assessment on the impact of their product on the QT interval. Dr. Winchell noted the following in her review:

Careful evaluation of the effects of buprenorphine on cardiac conduction was not performed during the development programs for Suboxone or Subutex. Based on in vitro binding studies, buprenorphine was not expected to have cardiac conduction effects. However, a thorough QT (TQT) study was performed in a more-recent development program for a transdermal buprenorphine product used for analgesia. In that study, a dose of 40 mcg/hour prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points. This signal for QT prolongation was considered to meet the threshold for regulatory concern, but was not of clear clinical significance. The dose studied was significantly lower than the dose used for treating drug addiction; however, the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has not yet been evaluated in formal thorough QT studies.

Dr. Winchell also noted that sponsors of new formulations of buprenorphine are being informed that thorough QT studies would be required for their NDAs, but that these studies could be conducted as post-approval study. Teva will also be informed of this requirement.

#### Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Qiu and Xu that there are no clinical pharmacology issues that would preclude approval of this application.

## **6. Clinical Microbiology**

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

## **7. Clinical/Statistical – Efficacy**

As noted by Dr. Winchell in her review, the Applicant was not required to submit additional data demonstrating the clinical efficacy of buprenorphine.

#### Outstanding or Unresolved Issues

I concur with the overall conclusion reached by Dr. Winchell that there are no efficacy concerns that would preclude approval of this application.

## **8. Safety**

Because the application did not propose a novel dosage form, route of administration or new dose, the Applicant was not required to submit additional safety data. Dr. Winchell did review the studies that were submitted in support of this application for any unexpected safety findings – as noted by Dr. Winchell in her review, these studies were not conducted by the Applicant under an IND, and the Applicant did not seek any input from the Agency prior to conducting the studies. Dr. Winchell was particularly interested in evaluating whether 16 mg of buprenorphine could be effectively blocked by naltrexone.

The number of subjects enrolled in the studies is summarized as follows (adapted from Dr. Winchell's review):

- Study 300759 (Single-Dose, Open-Label, cross-over design)
  - 16 mg film vs two Suboxone 8 mg films
  - N = 80; completers = 59

- 4 Single-Dose treatments with 14 day washout
- Study 4001650 (Single-Dose, Open-Label, cross-over design)
  - 16 mg film, effect of temperature
  - N = 24, completers = 20
  - 3 Single-Dose treatments with 14-day washout
- Study 4001651 (Single-Dose, Open-Label, cross-over design)
  - 16 mg film, effect of pH
  - N = 24, completers = 20
  - 3 Single-Dose treatments with 14-day washout

Dr. Winchell noted that 127 healthy volunteers participated in the studies, with 44 subjects receiving three doses of the Applicant's product, and 73 subjects receiving two doses of the Applicant's product.

There were no deaths, serious adverse events (SAEs) or severe events reported. There were 14 dropouts after study drug – all due to vomiting. Of these, 3 occurred after naltrexone (which also causes vomiting) but before study drug.

The following table, adapted from the Applicant's Summary of Clinical Safety, contains the adverse events occurring in 5% or more of the subjects in the three studies.

System organ class Preferred term	Study 3007599 (N=80)			Study 4001650 (N=24) <sup>a</sup>				Study 4001651 (N=24) <sup>a</sup>			
	Predose <sup>b</sup> (N=80) n (%)	A: bup + nal <sup>c</sup> (N=79) n (%)	B: SUB <sup>d</sup> (N=79) n (%)	Predose <sup>b</sup> (N=24) n (%)	A: cold beverage (N=23) n (%)	B: hot beverage (N=23) n (%)	C: room temp H <sub>2</sub> O (N=22) n (%)	Predose <sup>b</sup> (N=24) n (%)	A: low pH beverage (N=23) n (%)	B: high pH beverage (N=24) n (%)	C: room temp H <sub>2</sub> O (N=23) n (%)
Number of subjects with at least 1 AE	15 (18.8)	46 (58.2)	46 (58.2)	6 (25.0)	10 (43.5)	11 (47.8)	9 (40.9)	5 (20.8)	13 (56.5)	11 (45.8)	7 (30.4)
Gastrointestinal disorders	14 (17.5)	37 (46.8)	34 (43.0)	5 (20.8)	9 (39.1)	10 (43.5)	8 (36.4)	3 (12.5)	7 (30.4)	8 (33.3)	5 (21.7)
Nausea	12 (15.0)	31 (39.2)	31 (39.2)	5 (20.8)	6 (26.1)	6 (26.1)	6 (27.3)	3 (12.5)	5 (21.7)	5 (20.8)	4 (17.4)
Vomiting	2 (2.5)	19 (24.1)	21 (26.6)	0 (0)	3 (13.0)	2 (8.7)	6 (27.3)	0 (0)	3 (13.0)	3 (12.5)	3 (13.0)
Paraesthesia oral	0 (0)	1 (1.3)	1 (1.3)	0 (0)	1 (4.3)	2 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain	0 (0)	6 (7.6)	2 (2.5)	0 (0)	0 (0)	2 (8.7)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)

System organ class Preferred term	Study 3007599 (N=80)			Study 4001650 (N=24) <sup>a</sup>				Study 4001651 (N=24) <sup>a</sup>			
	Predose <sup>b</sup> (N=80) n (%)	A: bup + nal <sup>c</sup> (N=79) n (%)	B: SUB <sup>d</sup> (N=79) n (%)	Predose <sup>b</sup> (N=24) n (%)	A: cold beverage (N=23) n (%)	B: hot beverage (N=23) n (%)	C: room temp H <sub>2</sub> O (N=22) n (%)	Predose <sup>b</sup> (N=24) n (%)	A: low pH beverage (N=23) n (%)	B: high pH beverage (N=24) n (%)	C: room temp H <sub>2</sub> O (N=23) n (%)
Nervous system disorders	5 (6.3)	26 (32.9)	25 (31.6)	3 (12.5)	5 (21.7)	7 (30.4)	5 (22.7)	1 (4.2)	5 (21.7)	6 (25.0)	5 (21.7)
Dizziness	1 (1.3)	15 (19.0)	15 (19.0)	1 (4.2)	4 (17.4)	2 (8.7)	3 (13.6)	0 (0)	2 (8.7)	4 (16.7)	3 (13.0)
Headache	2 (2.5)	12 (15.2)	11 (13.9)	1 (4.2)	2 (8.7)	6 (26.1)	4 (18.2)	0 (0)	3 (13.0)	3 (12.5)	3 (13.0)
Somnolence	3 (3.8)	3 (3.8)	6 (7.6)	1 (4.2)	0 (0)	1 (4.3)	0 (0)	1 (4.2)	1 (4.3)	0 (0)	1 (4.3)
Psychiatric Disorders	0 (0)	3 (3.8)	10 (12.7)	0 (0)	0 (0)	2 (8.7)	0 (0)	1 (4.2)	0 (0)	0 (0)	2 (8.7)
Euphoric mood	0 (0)	1 (1.3)	5 (6.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.7)

<sup>a</sup> All subjects were administered buprenorphine/naloxone, 16 mg/4 mg.

<sup>b</sup> Adverse events that occurred after naltrexone and before a dose of study drug.

<sup>c</sup> Buprenorphine/naloxone dose was 16 mg/4 mg.

<sup>d</sup> Suboxone dose was 2 × 8 mg/2 mg.

AE = adverse event; bup = buprenorphine; H<sub>2</sub>O = water; nal = naloxone; SUB = Suboxone; temp = temperature.

Note: Subjects were counted only once in each preferred term category and only once in each system organ class category.

There were no findings of concern in the laboratory or EKG evaluations, or vital signs. Dr. Winchell concluded that the safety data from these studies provided little new information about the systemic safety of buprenorphine, although it did suggest that 16 mg of buprenorphine could be safely studied in monitored, naltrexone-blocked volunteers.

With respect to local tolerability of the Applicant's product, the single-dose design of the studies provided limited information. Dr. Winchell noted that dry mouth was reported by some patients; one patient reported an event of lip ulceration during treatment with the reference product and there were occasional events of oral paresthesia (one with Suboxone, four (across all studies) with the Applicant's product).

#### Outstanding or Unresolved Issues

I concur with Dr. Winchell that there are no safety concerns that would preclude approval of this application.

## 9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

## 10. Pediatrics

The Applicant requested a waiver of the requirements for the studies stipulated by the Pediatric Research Act (PREA) of 2003. The rationale for the neonate age group (0 to 5 weeks of age) was based on safety concerns: although buprenorphine could theoretically be used to treat neonatal abstinence syndrome, the product contains naloxone, which would not have a purpose in this clinical scenario, and would have potential safety concerns.

With respect to the older age groups (older than 5 weeks and up to 16 years of age), the Applicant indicated that such studies would be impossible or highly impracticable, due to the low prevalence of opioid abuse and dependence in this patient population.

The Division concurred with the Applicant's rationale, and presented the information to the Pediatric Review Committee (PeRC), which agreed that a full waiver should be granted.

## 11. Other Relevant Regulatory Issues

### Reference Drug Identified for 505(b)(2) Purposes

The Applicant has referenced the Suboxone film application (NDA 22410) for purposes of relying on the Agency's previous finding of safety and efficacy of a buprenorphine/naloxone.

### Financial Disclosure

The Applicant submitted financial disclosure forms for the investigators involved in the pharmacokinetic studies. Dr. Winchell reviewed them and no concerns were identified.

### Risk Evaluation and Mitigation Strategy (REMS)

The reference product (Suboxone film) is marketed under a REMS. Generic products are approved with a comparable, shared REMS, identified as the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS. The BTOD REMS contains the same goals and elements as the Suboxone REMS, and NDA holders have the option of participating in this shared REMS program.

The goals and components of the BTOD REMS, which the Applicant has agreed to join, are listed below:

The goals of the REMS are to:

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

REMS Elements:

3. Medication Guide
4. Elements to Assure Safe Use
  - a. Safe use Conditions
  - b. Monitoring

5. Implementation System
6. Timetable for Submission of Assessments

Materials for Prescribers:

1. Dear Prescriber Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers
3. Appropriate Use Checklist

Materials for Pharmacists:

1. Dear Pharmacist Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists

Materials for Patients:

Medication Guide

Outstanding or Unresolved Issues

There are no outstanding or unresolved regulatory issues that would preclude approval of this application.

## 12. Labeling

Consultations were obtained from the following divisions: the Division of Pediatric and Maternal Health (DPMH), the Division of Medication Error Prevention and Analysis (DMEPA), Division of Risk Management (DRISK), and the Controlled Substance Staff.

The Applicant's NDA only proposed one strength, 16 mg buprenorphine/4 mg naloxone, therefore several aspects of the reference drug's label were not applicable – for example, information for use as initial treatment and information about tapering. Dr. Winchell noted that there were several differences between the Applicant's proposed labeling and the labeling found acceptable by the review team. Dr. Winchell's review cited the following examples:

- Indication changed from “(b) (4)” to “maintenance treatment of opioid dependence” (b) (4)
- In the Dosage and Administration section, and elsewhere, references to dose titration were modified to note that dose adjustments would require use of a different product. For example, the D&A section reads:

The dosage of Buprenorphine and Naloxone Sublingual Film may need to be adjusted (b) (4) to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

(b) (4) (16 mg / 4 mg) should only be used after induction and stabilization of the patient, and the patient has been titrated to a dose of 16 mg using another marketed product.

- Certain language specific to another product was removed from the Clinical Trials Experience section of the Adverse Reactions.
- Sections on use in Pregnancy and Lactation were revised to conform with PLLR requirements and to reflect the recent review of literature conducted in association with a PLLR supplement for the reference product.
- New required information about neonatal opioid withdrawal syndrome and new safety warnings pertaining to all opioids were added.
- While the representation of the individual pouches as child-resistant was retained, (b) (4).
- Editorial changes to conform with best labeling practices were made throughout.

Because the application was not ready for approval during this review cycle, the review team will convey the proposed modifications to the label to the Applicant during the next review cycle.

### 13. Decision/Action/Risk Benefit Assessment

#### Regulatory Action

Complete Response due to the inability to conduct a routine inspection of the drug product manufacturing site because the site was not ready for inspection.

#### Risk:Benefit Assessment

A favorable risk:benefit assessment of a buprenorphine/naloxone combination product for maintenance treatment of opioid dependence has already been demonstrated in the reference product, the Suboxone film. The Applicant, through the pharmacokinetic studies, has demonstrated that their product has the same systemic exposure as the Suboxone film; therefore, the efficacy and benefit is expected to be comparable.

The Applicant's product does not appear to present any new safety concerns. However, it also does not contain any safety benefit compared to the reference product, and must therefore also be subject to a REMS program.

#### Recommendation for Postmarketing Risk Management Activities

The product is subject to the BTOD REMS, consisting of a Medication Guide, Elements to Assure Safe Use, and Implementation System.

#### Recommendation for other Postmarketing Study Commitments

No commitments are required.

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/s/  
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RIGOBERTO A ROCA  
09/30/2016

## Cross-Discipline Team Leader Review

<b>Date</b>	9/30/16
<b>From</b>	Celia Winchell, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	208042
<b>Applicant</b>	Teva Pharmaceuticals
<b>Date of Submission</b>	11/30/2015
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<b>Proposed Indication(s)</b>	(b) (4) of opioid dependence
<b>Recommended:</b>	<i>Complete Response</i>

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## 1. Introduction

This application is for a new buprenorphine/naloxone combination product for the maintenance treatment of opioid dependence, referencing the approved product Suboxone (buprenorphine/naloxone) sublingual film (NDA 22410<sup>1</sup>, Indivior<sup>2</sup>) through the 505(b)(2) pathway. No proprietary name has been proposed.

The recommended dose of Suboxone film for most patients is 16 mg buprenorphine once daily, delivered as two films containing 8 mg buprenorphine and 2 mg naloxone each. Teva has developed a 16 mg film that has been shown to be bioequivalent to two 8 mg Suboxone films, and the application rests on the Agency's previous findings of safety and efficacy of Suboxone.

Although Suboxone film is marketed in strengths of 2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; and 12 mg/3 mg, Teva proposes only one dosage strength (16 mg/4 mg) in this application. Teva has filed ANDAs for other products equivalent to the marketed strengths of Indivior's products.

A comparative bioavailability study was performed comparing the 16 mg/4 mg film to the 8/2 mg Suboxone film.

Teva's product should be used in patients who have already begun treatment using other products that are titratable, and whose dose requirement is 16 mg/day.

This review will briefly summarize the clinical pharmacology findings and safety findings from the pharmacokinetic studies in healthy, naltrexone-blocked volunteers.

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<sup>1</sup> 22410, in turn, references NDA 20732 for Subutex buprenorphine sublingual tablets and 20733 for Suboxone buprenorphine/naloxone sublingual tablets, NDAs which are held by Indivior but no longer marketed.

<sup>2</sup> Formerly Reckitt & Colman and subsequently Reckitt Benckiser

## 2. Background

Buprenorphine is a partial agonist at the  $\mu$ -opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence.<sup>3</sup> Three other transmucosal formulations have subsequently been approved for opioid dependence, as well as two transdermal products and one transmucosal product for pain. Approximately (b) (4) prescriptions were dispensed from outpatient retail pharmacies and approximately (b) (4) patients received a dispensed prescription for buprenorphine tablets or films during 2014.<sup>4</sup>

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the  $\mu$ -opioid receptor. First, buprenorphine had been shown to have a ceiling effect for respiratory depression, suggesting that it would be “impossible to overdose” on buprenorphine. Second, initial clinical evaluations of buprenorphine’s ability to produce physical dependence led to the conclusion that physical dependence to buprenorphine, if it developed, was associated with a mild withdrawal syndrome. Third, it was expected to have limited attractiveness as a drug of abuse relative to full agonists.<sup>5</sup>

Buprenorphine was expected to have limited abuse potential for two reasons. First, due to its partial agonist properties, the euphorogenic effects of buprenorphine were understood to reach a “ceiling” at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. Second, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal if they use buprenorphine. These features were expected to limit its attractiveness as a drug of abuse for patients and for illicit use.

In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients.

As a partial agonist, buprenorphine has the potential to precipitate withdrawal symptoms when used by an individual who is dependent on full opioid agonists such as heroin, methadone, or oxycodone. However, most transmucosal buprenorphine products intended for addiction treatment are co-formulated with naloxone. The naloxone is intended to be inactive when the product is used as intended, but to add an additional measure of abuse deterrence by

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<sup>3</sup> Subutex, buprenorphine sublingual tablets (Reckitt Benckiser NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser NDA 20733). Naloxone is intended to further deter abuse by the intravenous route by precipitating withdrawal if the product is injected by persons dependent on full agonists.

<sup>4</sup> IMS National Prescription Audit and Total Patient Tracker, Year 2014, extracted 12/15

<sup>5</sup> Many of these beliefs have subsequently been found to have been erroneous, or at least overstated, but these were the generally-held views about buprenorphine’s pharmacology at the time it was being developed.

precipitating more severe withdrawal if the product is crushed and injected by an individual dependent on full agonists.

The Teva product was developed without an IND. Teva originally interacted with the Division via a pre-NDA meeting request in May 2013. At that time, they were provided with responses to questions regarding necessary stability data and pharmacology-toxicology data, and advised to perform evaluations of the effect of temperature and pH on the bioavailability of their product. They were also advised to provide the dimensions of the 16 mg product and explain how it fits onto the dorsal surface of the tongue or onto the floor of the mouth. Additional questions were submitted in March 2014, and in response the firm was provided with preliminary assessments that no further toxicology studies appeared needed, that additional studies of abuse liability would not be needed, and that a waiver from required pediatric studies under PREA was possible.

Teva originally submitted the Application on October 29, 2014 but the Division issued a Refusal to File letter because the application did not contain required components of an NDA submission, including an Introduction, Clinical Overview, Clinical Summary, Integrated Summary of Safety and Efficacy, or an overall Table of Contents for the submission. Also missing were datasets of adverse events and required narratives, an integrated summary of the risks and benefits of the product, and a section addressing abuse liability.

## **2.2 Legal and Regulatory Issues Constraining Buprenorphine Treatment**

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing this product must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements.

Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974. The current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases. Buprenorphine may also be administered to patients at OTPs.

Buprenorphine treatment is covered Title XXXV of the Children's Health Act of 2000 (P.L. 106-310), which provides a "Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients." This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8 hour training courses are provided by various physician organizations (e.g., APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine.

### 3. CMC/Device

The Chemistry review was conducted by a Quality Review Team led by Ciby Abraham, Ph.D. and comprising the following reviewers:

Drug Substance	<b>Erika Englund</b>
Drug Product	<b>Xiaobin Shen</b>
Process	<b>Pei-I Chu</b>
Microbiology	<b>Eric Adeeku</b>
Facility	<b>Rebecca Dombrowski</b>
<b>Biopharmaceutics</b>	<b>Vidula Kolhatkar/Kelly Kitchens</b>

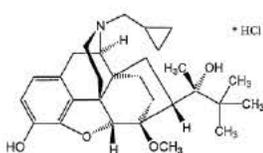
#### 3.1 General product quality considerations

##### 3.1.1. Drug Substances

The first drug substance is buprenorphine HCl, manufactured by Teva Czech Industries s.r.o. (TCI) and is referenced in DMF# 16419, which was reviewed and found acceptable.

Molecular formula:  $C_{29}H_{41}NO_4 \cdot HCl$

Molecular Weight: 467.6 (Base) 504.1 (salt)

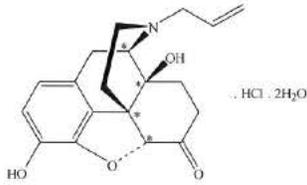


Buprenorphine HCl is a white or almost white crystalline powder. Only one crystal form is found.

The second drug substance is naloxone HCl, manufactured by (b) (4) and is referenced in DMF# (b) (4), which was reviewed and found acceptable. One impurity with a structural alert, (b) (4), was identified. This impurity is controlled to (w) (4) ppm in the drug substance specifications. This corresponds to a total daily intake of (b) (4) µg. This is below the 1.5 µg daily intake limit described in ICH M7 for a lifetime of treatment.

Molecular formula:  $C_{19}H_{21}NO_4 \cdot HCl$ .

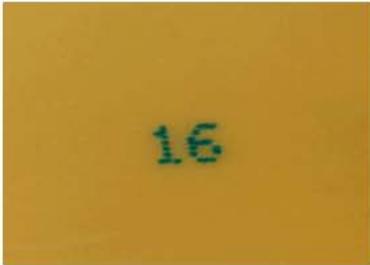
Molecular weight: 399.9



The naloxone drug substance is a white solid that is soluble in water.

### 3.1.2 Drug Product

The drug product is a flexible rectangular film with uniformly distributed orange color, imprinted in Blue ink (b) (4) (16 may appear to be green in color), and is packaged in individual (b) (4) laminated foil pouches. The dimensions are 22.3 mm x 25.4 mm. The reference product (described in the submission as similar in dimension) is 0.875" x 0.5" (i.e., 22 mm x 13 mm). However, another approved dosage form of the Indivior film, the 4 mg/1 mg film, is approximately the same dimensions as the proposed product. The 4 mg film was approved without clinical studies but no specific complaints related to placement in the mouth have been noted.

Teva's proposed Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg	
<b>Appearance:</b>	<p>Flexible rectangular film with uniformly distributed orange color. Imprint in Blue ink (b) (4) (16 may appear to be green in color). The film can be removed from the pouch as an intact piece.</p> <div style="text-align: center;">  </div>
<b>Physical Descriptions:</b>	<p><b>Unit Dimensions:</b> 22.3 mm X 25.4 mm <b>Thickness:</b> ~ 150 µm <b>Weight:</b> 93 mg</p>

Except the flavoring agent, colorants and ink, the two actives and all other excipients are of USP or NF grade. The colorants are FDA certified. The flavoring agent, ink, and excipients used above the levels found in the Inactive Ingredient database are supported with corresponding toxicological reports, which are deemed acceptable by pharm/tox reviewer Dr. Elizabeth Bolan.

The drug product manufacturing process involves (b) (4)

According to the CMC review team, the Applicant reported that (b) (4) are considered high risk factors to product content uniformity; critical process parameters such as (b) (4) will affect product assay results, and the Applicant plans to evaluate and establish acceptable (b) (4) during process scale-up and process validation.

During review, the CMC team noted that:

**The applicant has conducted risk assessment for each unit operation. Development data were provided to justify the selected process parameters and in-process testing specification.** (b) (4)

**The applicant concluded in their corrective action that “the process to manufacture the product is not fully optimized. All the observations/deviations from the pilot scale batches will be evaluated to finalize the commercial manufacturing process”.**

A number of other questions and issues related to manufacture were identified, and responses to information requests were not adequate to resolve them. The Applicant indicated that work on the scale-up process was ongoing.

On July 22, 2016 when FDA sought to inspect the manufacturing site, inspectors were informed that the manufacturing site, LTS (Lohman Therapeutic Systems) was not ready for inspection and that the site did not have the equipment ready. The review team noted that this indicates that the Applicant lacks knowledge of the commercial manufacturing process and process parameters that may affect critical quality attributes of the product. Without the manufacturing site ready for inspection, the process group could not complete their review and identified several concerns related to the manufacturing process, focused on critical attributes of (b) (4) and content uniformity. The process team conveyed their concerns to the inspection team and this will be addressed in the next inspection of LTS.

The drug product specifications were deemed acceptably justified and suitable. The reviewers noted that the acceptance limit for one excipient, BHA, is not consistent between the release and stability specifications because it is anticipated to be consumed over the product shelf life.

The CMC review team indicated that a request for the revision of the BHA acceptance limit should be made in the next review cycle.

The pouch in which the product is sealed is intended to provide a child resistant barrier. A child resistance study report was provided and found to be supportive of this claim, allowing it to be included in labeling

### 3.1.4 Expiration Dating

The proposed shelf-life is 24 months, which was found to be supported by the provided stability data.

### 3.2 Facilities review/inspection

Approval of the drug substance manufacturing sites, Teva Czech Industries s.r.o., and (b) (4), was recommended based on file review and capabilities and history of the site. (b) (4) An additional site named for the manufacture and testing of the Naloxone HCl drug, (b) (4) was recommended for approval based on inspectional history, as were control testing laboratories.

However, as noted above, the site identified for manufacture of the drug product, LTS Lohmann Therapy Systems Corp, was not ready for inspection and a recommendation to withhold approval was made. The site was similarly “not ready” for inspection for related ANDAs for lower strength buprenorphine/naloxone films in December 2015<sup>6</sup>.

Other sites (contract packagers and labelers) were recommended for approval.

## 4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review was performed by Elizabeth Bolan, Ph.D., supervised by R. Daniel Mellon, Ph.D.

No new nonclinical studies were required for this NDA and no studies were conducted. The excipients in this formulation can be found in higher amounts in products approved for chronic use and do not pose any toxicologic concerns. All impurities/degradants in the drug substances and drug product are controlled at acceptable levels. There are no unique nonclinical issues with this product as compared to other sublingual formulations of its individual components

In the label, changes were recommended to comply with Pregnancy and Lactation Labeling Rule requirements and were aligned with a recent review of the NDA for the referenced product.

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<sup>6</sup> Ownership of these two ANDAs, 205299 for Buprenorphine and Naloxone Sublingual Film, 2 mg/0.5 mg and 8 mg/2 mg and 205806 for Buprenorphine and Naloxone Sublingual Film, 4 mg/1 mg and 12 mg/3 mg, was transferred to Dr. Reddy’s Laboratories in August 2016 and they remain under review.

## 5. Clinical Pharmacology/Biopharmaceutics

### 5.1 General Background

This overview of buprenorphine and buprenorphine/naloxone clinical pharmacology is taken largely from the approved labeling for NDA 20-723 and 20-733.

Pharmacokinetics of buprenorphine and naloxone (as Suboxone) show wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability is low. Both  $C_{max}$  and AUC of buprenorphine show dose linearity in the range of 4 to 16 mg, but not dose proportionality. The table below from the labeling for Suboxone and Subutex shows the PK parameters. Buprenorphine has a mean elimination half-life of 37 hours; naloxone has a half-life of 1.1 hours. Naloxone does not affect the PK

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation. Cytochrome P-450 3A4 (CYP3A4) inhibitors may increase plasma concentrations of buprenorphine.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group. Buprenorphine is eliminated in urine (30%, primarily conjugated) and feces (69%, primarily free buprenorphine and norbuprenorphine).

Hepatic impairment differentially affects the PK of buprenorphine and naloxone. In subjects with mild hepatic impairment, the changes in mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone are not clinically significant and no dosing adjustment is needed in patients with mild hepatic impairment. However, in subjects with moderate and severe hepatic impairment, mean  $C_{max}$ ,  $AUC_{0-last}$ , and half-life values of both buprenorphine and naloxone are increased, with the effects on naloxone being greater than that on buprenorphine. In patients with severe hepatic impairment, the increase in naloxone exposure is 10-fold or greater, and this could have implications for both safety and efficacy.

Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

Renal impairment does not affect buprenorphine PK. The effects of renal failure on naloxone PK are unknown.

### 5.2 Clinical Pharmacology Findings

The clinical pharmacology review was conducted by Wei Qui, Ph.D., supervised by Yun Xu, Ph.D. The clinical pharmacology database consists of a pivotal comparative bioavailability study (Study 3007599), effect of temperature study (Study 4001650), and effect of pH study (Study 4001651). The final to-be-marketed formulation was used in all these PK Studies.

### 5.2.1 Bioequivalence of Teva's Product to Reference Product

In Study 3007599, the Applicant's product was compared to the reference product, Suboxone sublingual film, 8/2 mg x 2 films. Note there is no 16/4 mg strength for Suboxone sublingual film. Teva buprenorphine/naloxone sublingual film 1 x 16/4 mg exhibited equivalent systemic exposure ( $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ ) to buprenorphine and naloxone in comparison to the listed drug, Suboxone sublingual film 2 x 8/2 mg, with the 90% confidence interval (CI) of the geometric mean ratios for  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  values of buprenorphine and naloxone for Teva buprenorphine/naloxone sublingual film to Suboxone sublingual film falling within the bioequivalence limits of 80 to 125%.

The PK parameters and statistical comparisons are shown in the tables below (reproduced in Dr. Qiu's review from the study report).

**Table 3** Summary of the PK parameters of Buprenorphine following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
$C_{max}$ (pg/mL)	138	6223	3026	133	6752	3004
$T_{max}$ (h)	138	1.25	0.33, 3.00	133	1.25	0.33, 3.00
$AUC_{last}$ (h.pg/mL)	138	57392	22572	133	62350	22410
$AUC_{inf}$ (h.pg/mL)	138	60052	23463	133	65314	23398
$T_{1/2}$ (h)	138	34.61	9.75	133	36.62	11.46

Note:  $T_{max}$  shown as median (min, max).

**Table 4** Summary of the PK parameters of Norbuprenorphine following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
$C_{max}$ (pg/mL)	137	2983	1673	133	3156	1602
$T_{max}$ (h)	137	1.00	0.33, 48.00	133	1.00	0.49, 48.00
$AUC_{last}$ (h.pg/mL)	137	94096	39148	133	96584	38942
$AUC_{inf}$ (h.pg/mL)	136	104070	44896	132	107934	48882
$T_{1/2}$ (h)	136	35.09	16.32	132	37.24	20.72

Note:  $T_{max}$  shown as median (min, max).

**Table 5** Summary of the PK parameters of Naloxone following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
C <sub>max</sub> (pg/mL)	138	439	245	133	413	237
T <sub>max</sub> (h)	138	0.75	0.33, 2.00	133	0.75	0.33, 2.50
AUC <sub>last</sub> (h.pg/mL)	138	1015	521	133	957	449
AUC <sub>inf</sub> (h.pg/mL)	138	1046	523	133	985	451
T <sub>1/2</sub> (h)	138	6.56	6.16	133	5.85	4.39

Note: T<sub>max</sub> shown as median (min, max).

**Table 6** Summary of the PK parameters of Total Naloxone following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
C <sub>max</sub> (ng/mL)	138	55.6	24.0	133	54.3	23.0
T <sub>max</sub> (h)	138	0.75	0.33, 6.03	133	0.75	0.33, 16.00
AUC <sub>last</sub> (h.ng/mL)	138	108.2	37.3	133	107.4	38.5
AUC <sub>inf</sub> (h.ng/mL)	138	111.9	37.7	132	111.0	38.8
T <sub>1/2</sub> (h)	138	7.90	3.82	132	8.06	4.33

Note: T<sub>max</sub> shown as median (min, max).

The statistical analysis results for the assessment of relative bioavailability are presented in Dr. Qiu's **Tables 7** and **8**, showing that all parameters fell within the bioequivalence limits of 80 to 125%. These analyses employ the reviewer's requested average BE approach, rather than the Applicant's original reference-scaled BE procedure, because this was deemed more appropriate in light of the high intra-subject variability following administration of the reference product.

**Table 7** Summary of the Statistical Analysis of PK Parameters of Buprenorphine Comparing 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Test) to 2 x 8/2 mg Suboxone Sublingual Film (Reference) (Study 3007599)

Variable	Geometric Mean		Ratio (%) (A/B)	90% CI	
	Treatment A (Teva Product) (N = 138)	Treatment B (Suboxone Film) (N = 133)		Lower	Upper
C <sub>max</sub> (pg/mL)	5424	6055	89.58	83.98	95.56
AUC <sub>last</sub> (h.pg/mL)	51945	58222	89.22	84.37	94.35
AUC <sub>inf</sub> (h.pg/mL)	54435	60918	89.36	84.56	94.43

**Table 8** Summary of the Statistical Analysis of PK Parameters of Naloxone Comparing 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Test) to 2 x 8/2 mg Suboxone Sublingual Film (Reference) (Study 3007599)

Variable	Geometric Mean		Ratio (%) (A/B)	90% CI	
	Treatment A (Teva Product) (N = 138)	Treatment B (Suboxone Film) (N = 133)		Lower	Upper
C <sub>max</sub> (pg/mL)	364.2	353.5	103.02	95.80	110.78
AUC <sub>last</sub> (h.pg/mL)	877.7	869.8	100.91	95.28	106.87
AUC <sub>inf</sub> (h.pg/mL)	912.6	898.6	101.55	96.11	107.31

### 5.2.3 Effect of Beverages

The PK program also included a study of the effects of co-administered liquids. Pretreatment with cold water did not affect systemic exposure; pre-treatment with hot water increased buprenorphine C<sub>max</sub> by 15% but did not affect other parameters for buprenorphine or for naloxone.

The evaluation of pH included pretreatment with a low pH beverage (Sprite soda, mean pH 3.34, range 3.33-3.36) and pretreatment with a “high pH beverage,” a solution of sodium bicarbonate which had a mean pH of 7.99 (range 7.94-8.02). The room temperature water used as a comparator had a pH of 7.51 (range 7.47-7.60), so that the evaluation of the impact of “high pH” may have been underestimated due to the small difference between the high pH condition and the control condition. Nevertheless, pretreatment with the bicarbonate solution

increased Naloxone  $C_{max}$  and AUC values by 142% and 89- 92%, respectively. Labeling instructions to avoid high pH beverages prior to dosing are warranted.

Following pretreatment with Sprite, buprenorphine  $C_{max}$  and AUC values were decreased by 14-15% and naloxone  $C_{max}$  and AUC values were decreased by 30-36% following drinking Sprite. Decreases in naloxone exposure are not a clinical concern because it is not intended to be active when the product is used as directed.

### **5.3 QT assessment**

No QT assessment was undertaken in this development program.

Careful evaluation of the effects of buprenorphine on cardiac conduction was not performed during the development programs for Suboxone or Subutex. Based on *in vitro* binding studies, buprenorphine was not expected to have cardiac conduction effects. However, a thorough QT (TQT) study was performed in a more-recent development program for a transdermal buprenorphine product used for analgesia. In that study, a dose of 40 mcg/hour prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points. This signal for QT prolongation was considered to meet the threshold for regulatory concern, but was not of clear clinical significance. The dose studied was significantly lower than the dose used for treating drug addiction; however, the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has not yet been evaluated in formal thorough QT studies. Such studies have been requested of Indivior as post-marketing requirements, but have not yet been completed. Although sponsors of other INDs to evaluate new formulations of buprenorphine have been informed that TQT studies would be required for their NDAs, but could be performed post-approval, Teva does not appear to have been so informed during their two pre-IND requests for guidance, which addressed specific questions posed by the Sponsor.

## **6. Clinical Microbiology**

N/A

## **7. Clinical/Statistical- Efficacy**

No new data on the clinical efficacy of buprenorphine were submitted.

## **8. Safety**

Because this is not a novel dosage form and route of administration for buprenorphine, no safety data were generated beyond the data from the PK studies in naltrexone-blocked healthy volunteers. The data from these studies is of interest primarily because it was not known whether a dose of 16 mg of buprenorphine could be completely blocked by naltrexone and

whether such studies could be done safely. (Teva did not perform these studies under IND and did not seek Agency input.)

The studies included

- 300759 BE Study (SD, OL, x-over)
  - 16 mg film vs two Suboxone 8 mg films
  - N = 80; completers = 59
  - 4 SD treatments w/14 day washout
- 4001650 BA Study (SD, OL, x-over)
  - 16 mg film, effect of temperature
  - N = 24, completers = 20
  - 3 SD treatments w/14-day washout
- 4001651 BA Study (SD, OL, x-over)
  - 16 mg film, effect of pH
  - N = 24, completers = 20
  - 3 SD treatments w/14-day washout

A total of 127 healthy volunteers participated in the studies; 44 had three doses of the Teva product and 73 had two doses.

There were no deaths, SAEs or severe events. There were 14 dropouts (all due to vomiting) after study drug. Of these, 3 occurred after naltrexone (which also causes vomiting) but before study drug.

In the pivotal bioequivalence study, more subjects in the Teva arm (9%) dropped out compared to the Indivior arm (4%).

The most commonly-reported adverse events are shown in the table below, from the Clinical Overview.

Cross Discipline Team Leader Review

System organ class Preferred term	Study 3007599 (N=80)			Study 4001650 (N=24) <sup>a</sup>				Study 4001651 (N=24) <sup>a</sup>			
	Predose <sup>b</sup> (N=80) n (%)	TEVA (N=79) n (%)	SUBOX (N=79) n (%)	Predose <sup>b</sup> (N=24) n (%)	COLD (N=23) n (%)	HOT (N=23) n (%)	Rm Temp (N=22) n (%)	Predose <sup>b</sup> (N=24) n (%)	Acid (N=23) n (%)	Base (N=24) n (%)	Neutral (N=23) n (%)
Gastrointestinal disorders	14 (17.5)	37 (46.8)	34 (43.0)	5 (20.8)	9 (39.1)	10 (43.5)	8 (36.4)	3 (12.5)	7 (30.4)	8 (33.3)	5 (21.7)
Nausea	12 (15.0)	31 (39.2)	31 (39.2)	5 (20.8)	6 (26.1)	6 (26.1)	6 (27.3)	3 (12.5)	5 (21.7)	5 (20.8)	4 (17.4)
Vomiting	2 (2.5)	19 (24.1)	21 (26.6)	0 (0)	3 (13.0)	2 (8.7)	6 (27.3)	0 (0)	3 (13.0)	3 (12.5)	3 (13.0)
Paraesthesia oral	0 (0)	1 (1.3)	1 (1.3)	0 (0)	1 (4.3)	2 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain	0 (0)	6 (7.6)	2 (2.5)	0 (0)	0 (0)	2 (8.7)	1 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
Nervous system disorders	5 (6.3)	26 (32.9)	25 (31.6)	3 (12.5)	5 (21.7)	7 (30.4)	5 (22.7)	1 (4.2)	5 (21.7)	6 (25.0)	5 (21.7)
Dizziness	1 (1.3)	15 (19.0)	15 (19.0)	1 (4.2)	4 (17.4)	2 (8.7)	3 (13.6)	0 (0)	2 (8.7)	4 (16.7)	3 (13.0)
Headache	2 (2.5)	12 (15.2)	11 (13.9)	1 (4.2)	2 (8.7)	6 (26.1)	4 (18.2)	0 (0)	3 (13.0)	3 (12.5)	3 (13.0)
Somnolence	3 (3.8)	3 (3.8)	6 (7.6)	1 (4.2)	0 (0)	1 (4.3)	0 (0)	1 (4.2)	1 (4.3)	0 (0)	1 (4.3)
Psychiatric disorders	0 (0)	3 (3.8)	10 (12.7)	0 (0)	0 (0)	2 (8.7)	0 (0)	1 (4.2)	0 (0)	0 (0)	2 (8.7)
Euphoric mood	0 (0)	1 (1.3)	5 (6.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8.7)

<sup>a</sup> All subjects were administered buprenorphine/naloxone, 16 mg/4 mg.

<sup>b</sup> Adverse events that occurred after naltrexone and before a dose of study drug.

<sup>c</sup> Buprenorphine/naloxone dose was 16 mg/4 mg.

<sup>d</sup> Suboxone dose was 2 × 8 mg/2 mg.

AE = adverse event; bup = buprenorphine; H<sub>2</sub>O = water; nal = naloxone; SUB = Suboxone; temp = temperature.

Note: Subjects were counted only once in each preferred term category and only once in each system organ class category.

Regarding vital signs and oxygenation, the following significant changes in respiratory rate and oxygenation were observed:

- 30759: 46 subjects had RR <10, no PO<sub>2</sub><90
- 4001650: 19 subjects had RR < 10, 1 had PO<sub>2</sub><90 but only pre-dose
- 4001651: 14 subjects had RR<10, no PO<sub>2</sub><90

There were no other findings of concern in lab, vital sign, or EKG evaluations. Although this provides little new information about the systemic safety of buprenorphine, it suggests that it is possible to study doses as high as 16 mg in suitably-monitored, naltrexone blocked volunteers.

Regarding local tolerability, these single-dose studies do not provide informative findings. Dry mouth was reported by some patients; one patient reported an event of lip ulceration during treatment with the reference product and there were occasional events of oral paresthesia (one with Suboxone, four (across all studies) with the Teva product).

Teva was asked to explain how the product fits onto the dorsal surface of the tongue or onto the floor of the mouth, and provided the following.

Taking into account the average size of the adult human tongue, which is roughly 4 inches long and 2 inches wide, and accounting for the separation of the left and right side of the tongue via the lingual septum, there is sufficient surface area for the placement of Teva's proposed sublingual film under the tongue, close to the base on the left or right side. It should be noted that there were no reported comments/complaints concerning the size of the film in relation to any of the studies conducted in support of Teva's application.

To further support the above claim, we include reference herein to another CDER-approved product in which the method of administration is identical to our proposed product and for which the product incorporates similar unit dimensions.

The other approved dosage form of the Indivior film, the 4 mg/1 mg film, is approximately the same dimensions as the proposed product. The 4 mg film was approved without clinical studies but no specific complaints related to placement in the mouth have been noted in FAERS.

## 9. Advisory Committee Meeting

*N/A*

## **10. Pediatrics**

Teva requested a full waiver of the pediatric studies required under the Pediatric Research Equity Act (PREA).

The Division concurred that based on the most recent prevalence estimates and current and previous feasibility assessments, studies in adolescents would be highly impracticable. The product would not be appropriate for treatment of neonatal withdrawal due to the presence of naloxone. This information was provided to the Pediatric Review Committee (PeRC), who agreed that a waiver should be granted.

## **11. Other Relevant Regulatory Issues**

### ***11.2 Risk Evaluation and Mitigation Strategy***

The reference product, Suboxone film is marketed under a REMS. Although the REMS provisions under FDAAA call for a single shared system, a waiver was granted because Reckitt Benckiser declined to participate in a single shared system, and the Agency determined that the benefits of the waiver (access to medication) outweighed the burden of having multiple programs. All ANDA-holders are obliged to participate in the shared system, known as the BTOD (buprenorphine-containing transmucosal products for opioid dependence) REMS, but NDA holders are not subject to this requirement. Two other NDA holders, Orexo, marketing Zubsolv buprenorphine/naloxone sublingual tablets under NDA 204242, and BDSI, marketing Bunavail buprenorphine/naloxone buccal film under NDA 205637 joined the BTOD REMS at the time of approval of their applications.

The Agency requested that Teva join the shared system REMS to reduce the burden on the healthcare system by limiting the number of REMS for this class of products to two, and Teva has arranged to do so.

The goals of the REMS are to:

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

REMS Elements:

1. Medication Guide
2. Elements to Assure Safe Use
  - Safe use Conditions
  - Monitoring
3. Implementation System
4. Timetable for Submission of Assessments

Materials for Prescribers:

1. Dear Prescriber Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers
3. Appropriate Use Checklist

Materials for Pharmacists:

1. Dear Pharmacist Letter
2. Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists

Materials for Patients:

1. Medication Guide

The materials have been updated to include a description of the Teva product. Some confusion may exist because the Teva product does not have a proprietary name and can therefore be confused with any references to the generic name, buprenorphine/naloxone. The materials were reviewed and revised by the Division of Risk Management. Revision of materials focused on ways to limit this confusion wherever possible.

### ***11.3 OSI Inspection***

Inspections were not requested because recent inspections of the same sites raised no concerns.

### ***11.4 Cardiac Conduction Effects***

A study of the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has been requested of Indivior, who markets the reference product, as post-marketing requirement (PMR), but has not yet been completed. Teva will be informed that a TQT study would be required for their NDA if the information is available to be incorporated by reference at the time of resubmission, but that the study could be performed post-approval.

### ***11.5 Financial Disclosures***

Financial disclosures were reviewed and identified no concerns.

## 11.5 Controlled Substances Staff Review

The Controlled Substances team did not identify any concerns specific to the dosage form pertinent to abuse liability or abuse deterrence. They observed that the 16 mg dose was sufficient to produce some symptoms of drug effect even in the presence of naltrexone block.

## 12. Labeling

Physician labeling was based on labeling for the reference product. Some aspects of the Suboxone film labeling, such as use as initial treatment and details about titration and taper, are not applicable to the Teva product because it is available in only one strength. Appropriate modifications to labeling were made to reflect these differences.

Some aspects of labeling, as revised by the review team, were also based on recent literature reviews of the use of buprenorphine in pregnancy by the Maternal Health Team, and updated reviews by the pharmacology-toxicology team to conform with the Pregnancy and Lactation Labeling Rule.

Throughout the labeling, the Teva product was referred to using title case (Buprenorphine and Naloxone Sublingual Film) to distinguish it from references to generic buprenorphine or naloxone, or information about the two drug substances separately or together, or in other formulations.

Key differences between the sponsor's proposed labeling and the labeling proposed by the review team include:

- Indication changed from “(b) (4)” to “maintenance treatment of opioid dependence” (b) (4)
- In the Dosage and Administration section, and elsewhere, references to dose titration were modified to note that dose adjustments would require use of a different product. For example, the D&A section reads:

The dosage of Buprenorphine and Naloxone Sublingual Film may need to be adjusted (b) (4) to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

(b) (4) (16 mg / 4 mg) should only be used after induction and stabilization of the patient, and the patient has been titrated to a dose of 16 mg using another marketed product.
- Certain language specific to another product was removed from the Clinical Trials Experience section of the Adverse Reactions.
- Sections on use in Pregnancy and Lactation were revised to conform with PLLR requirements and to reflect the recent review of literature conducted in association with a PLLR supplement for the reference product.

- New required information about neonatal opioid withdrawal syndrome and new safety warnings pertaining to all opioids were added.
- While the representation of the individual pouches as child-resistant was retained, (b) (4) [REDACTED].
- Editorial changes to conform with best labeling practices were made throughout.

The Division of Medication Error Prevention and Analysis also provided comments, recommending that instructions about (b) (4) be removed from the Pouch Label and Carton Labeling because (b) (4) [REDACTED].

They also recommended that the font size of the strength statement (i.e., “16 mg/4 mg”) be increased on the principal display panels and that the lot number and expiration date be included on the pouch label and carton labeling. The statement “For Maintenance Treatment” should be included on the principal display panel to increase the prominence of the message that the indication for this strength is for maintenance dosing.

### 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Complete Response
- Risk Benefit Assessment

In the pharmacokinetic studies, this product provided the same systemic exposure to buprenorphine and naloxone as the reference product, Suboxone film. Its efficacy and benefit is expected to be the same as the reference product. It does not present new safety concerns compared to the reference product. It similarly does not provide any major safety benefits to patients, and will likely be subject to diversion, misuse, and abuse similar to the reference product. A REMS misuse, abuse, and accidental overdose will be needed to ensure the benefits outweigh the risks.

The drug product manufacturer, LTS Lohmann Therapy Systems site located in NJ (FEI 1000121692) was not ready for inspection and a recommendation to withhold approval was provided by the Office of Compliance. There is inadequate CMC information to recommend approval. Therefore, a Complete Response is recommended.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The components of the REMS are a MedGuide, ETASUs, and implementation system.

- Recommendation for other Postmarketing Requirements and Commitments

A study of the effects of buprenorphine on cardiac conduction at doses used for addiction treatment should be required.

The following issues were identified by the CMC review team to be communicated to the Applicant to be addressed in the next review cycle.

1. You have stated in your application that (1) the (b) (4) are considered high risk factors to product content uniformity, (2) critical process parameters such as (b) (4) will affect product assay results, and (3) acceptable (b) (4) will be evaluated and established during process scale-up and process validation. Provide the commercial (b) (4) equipment information, the critical process parameters for (b) (4) the commercial manufacturing process.
2. Confirm that you will continue to perform the (b) (4) for the commercial batches. In addition, you have proposed to conduct the content uniformity test in the drug product specification. Provide justification that your sampling plan and acceptance criteria for the content uniformity test provides statistical assurance that batches of drug product will meet appropriate specifications and statistical quality control criteria.
3. You have selected (b) (4) film as a (b) (4) during the manufacturing of buprenorphine and naloxone sublingual film. Provide information on 6 OPQ-XOPQ-TEM-  
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The CMC review also indicated that a request for the revision of the BHA acceptance limit should be made in the next review cycle.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CELIA J WINCHELL  
09/30/2016