CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208042Orig1s000

SUMMARY REVIEW

Clinical Review
Cross-Discipline Team Leader Review and Division Director Review

Date	September 7, 2018
NDA/BLA # and Supplement#	208042
Applicant	Teva Pharmaceuticals
Date of Original Submission Receipt	November 30, 2015 Complete Response Letter issued on September 30, 2016
Date of Complete Response Submission Receipt	March 8, 2018
PDUFA Goal Date	September 8, 2018
Proprietary Name	CASSIPA sublingual film
Established or Proper Name	Buprenorphine and naloxone sublingual film
Dosage Form(s)	16 mg/4 mg
Applicant Proposed Indication(s)/Population(s)	Maintenance treatment of Opioid Depenedence
Applicant Proposed Dosing Regimen(s)	16 mg/4 mg
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*Maintenance treatment of Opioid Dependence*

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

CASSIPA (buprenorphine/ naloxone combination product) is indicated for maintenance treatment of opioid dependence . Approval of the application is recommended.

Opioid use disorder, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality, as well as to social and economic costs to society. Current treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Methadone has been associated with fatal overdoses in patients and in their household contacts, including children. Oral naltrexone (REVIA) and depot naltrexone (VIVITROL) cannot be initiated until patients are fully detoxified, and may not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with VIVITROL. Subdermal implant (PROBUPHINE) is suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg buprenorphine), requires surgical insertion and removal, and carries a risk of implant migration (with potentially serious consequences) or expulsion; depot buprenorphine (SUBLOCADE) carries serious risk if inadvertently or intentionally administered intravenously. Oral-transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily. Daily use agonist and partial agonist MAT products, including CASSIPA, are subject to diversion, misuse, abuse and accidental pediatric exposure

The recommended dose of Suboxone, the reference product, is 16 mg as a single daily dose, given as two 8 mg tablets or films. CASSIPA 16 mg has been demonstrated to be bioequivalent to two SUBOXONE 8 mg films. In the pharmacokinetic studies, this product provided the same systemic exposure to buprenorphine and naloxone as the reference product, Suboxone film. CASSIPA was submitted as a 505(b)(2) application rather than as a 505(j) application (ANDA) because the reference product is not marketed in a 16 mg format. The safety profile of buprenorphine is well-characterized, and CASSIPA is expected to have a safety profile similar to the reference product . 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.

Moderate-to-severe opioid use disorder is a serious and life-threatening condition and the need for more treatment options is clear. The identified safety concerns are outweighed by the potential benefit and can be managed with the proposed labeling and REMS. Teva will join with other companies participating in the shared REMS known as the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS.

The goal of the (BTOD) REMS is to:

1. Reduce the risk of accidental overdose, misuse and abuse
2. Inform prescribers, pharmacuists and patients of the serious risks with the products.

The following materials are part of the BTOD REMS**:**

1. Medication Guide
2. Dear Healthcare Provider REMS Letter
3. Dear Pharmacist REMS Letter
4. Appropriate Use Checklist
5. REMS Program Website

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Opioid use disorder or OUD, as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), is a chronic, relapsing disease characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and physical consequences. Moderate to severe OUD corresponds, roughly, to the DSM-IV diagnosis "opioid dependence," and to the widely-used term, "addiction." Mild OUD corresponds to the DSM-IV diagnosis "opioid abuse." - In 2016, the National Survey on Drug Use and Health determined that over 2.1 million Americans aged 12 and over met criteria for either opioid abuse or dependence. - In 2015, the CDC reported that drug overdose was the leading cause of accidental death in the US, with 52,404 lethal drug overdoses in 2015. Of these, 20,101 overdose deaths were related to prescription pain relievers, and 12,990 overdose deaths were related to heroin. - Goals of treatment vary for individual patients, but typically involves a substantial change in illicit drug use behavior sufficient to translate to clinical benefit.	Opioid use disorder, particularly if classified as moderate or severe, is a serious and life-threatening condition and contributes to increased rates of morbidity and mortality, as well as to social and economic costs to society.
Current Treatment Options	- Current treatment options include non-drug (behavioral) treatment, as well as medication-assisted treatment (MAT) with antagonists (naltrexone), agonists (methadone) or partial agonists (buprenorphine). o Methadone is available only at federally-registered opioid treatment programs (OTPs), and patients must visit the clinic daily for in-person dosing until they meet criteria for receiving gradually-increasing numbers of take-home doses. Methadone has been associated with fatal overdoses in patients and in their household contacts, including children. o Subdermal implant (PROBUPHINE) is suitable only for patients clinically stable on low-moderate dose of transmucosal buprenorphine (≤ 8 mg buprenorphine), requires surgical insertion and removal, and carries a risk of implant migration (with potentially serious consequences) or expulsion. o Sublocade is a depot monthly injection that can improve adherence to treatment and decrease the risk of diversion. Sublocade carries significant risk if intentionally or inadvertently administered intravenously. While on Sublocade, if rapid reduction or discontinuation of buprenerphin is required, there are limited possibilities for surgical removal. Patients developing intolerance to buprenorphine effects will require long-term monitoring by a health care. o Oral naltrexone (REVIA) and depot naltrexone (VIVITROL) cannot be initiated until patients are fully detoxified, and may not be suitable or acceptable for all patients. Severe, and potentially serious, precipitated withdrawal can occur when naltrexone treatment is initiated. Serious injection site reactions requiring surgical intervention have been reported with VIVITROL. o Oral-transmucosal buprenorphine and buprenorphine/naloxone products and oral naltrexone products are intended to be self-administered by the patient daily ▪ Limitations of daily use products include poor adherence, fluctuating	The recommended dose of Suboxone is 16 mg as a single daily dose. Currently there are no transmucosal products that contain buprenorphine 16 mg in one dose. CASSIPA 16 mg has been demonstrated to be bioequivalent to two SUBOXONE 8 mg films and will provide ease of use for patients requiring buprenorphine 16 mg daily.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	plasma concentrations, intentional “drug holidays,” as well as patient convenience issues. ▪ Daily use agonist and partial agonist MAT products including CASSIPA are subject to diversion, misuse, abuse and accidental pediatric exposure	
Benefit	- The active ingredient, buprenorphine, has been approved for opioid dependence treatment since 2002. The recommended dose for the treatment of opioid dependence is 16 mg/day.	CASSIPA has been shown to be bioequivalent to two 8 mg doses of Suboxone Film, which is approved for use in the treatment of opioid dependence.
Risk and Risk Management	- The active ingredient, buprenorphine, has been marketed since 1981 and has been approved for opioid dependence treatment since 2002. The safety profile of CASSIPA is consistent with the reference product, Suboxone. - Safety concerns related to buprenorphine include hepatic effects, cardiac conduction effects, allergy/anaphylaxis, and general effects of the opioid class (e.g. respiratory depression, CNS depression, etc.) - CASSIPA will not be appropriate for initiating buprenorphine treatment, because lower doses are required to safely begin treatment in patients dependent on full agonists.	In the pharmacokinetic studies, this product provided the same systemic exposure to buprenorphine and naloxone as the reference product, Suboxone film. It is suitable for patients who have already begun buprenorphine treatment and for whom the 16 mg dose is appropriate. 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

2. Background

This application is a resubmission for a buprenorphine/ naloxone combination product for maintenance treatment of opioid dependence. The proposed proprietary name Cassipa, and is found to be acceptable.

The application was reviewed in 2016 and a Complete Response citing CMC concerns was issued. CMC issues are resolved in this cycle and the focus of this review cycle has been to harmonize the label and REMS with the approved buprenorphine/naloxone combination products. Much of this review is taken from Dr. Winchell's 2016 CTDL review. Buprenorphine is a partial agonist at the μ-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[1]. Three other transmucosal formulations, one implant and one depot subcutaneous injection have subsequently been approved for opioid dependence, as well as one transdermal product and one transmucosal productfor 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 2016.[2]

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 μ-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.[3]

Buprenorphine was expected to have limited abuse potential for two reasons. First, due to its partial agonist properties, the euphorigenic 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.

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[1] 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.

[2] IMS National Prescription Audit and Total Patient Tracker, Year 2016, extracted 8/17

[3] 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.

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 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 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.

The application was resubmitted on 11/30/2015 and a Complete Response was issued due to CMC concerns. The manufacturing site was not ready for inspection and as a result the quality of the product could not be adequately established.

3. Product Quality

The Drug product is a sublingual film comprising 16mg of buprenorphine and 4mg of naloxone. It is an immediate release formulation which releases both active ingredients within (b) (4) minutes. The films are 22.3 mm x 25.4 mm with a thickness of 150um and a weight of 93mg. Each film is packaged (b) (4) in a child resistant (b) (4) pouch. The pouch comprises (b) (4) . Sufficient stability data is provided to support an expiry of 24 months when stored under the following conditions:
"Store at (b) (4); excursions permitted between 15° and 30°C (59° and 86°F). (b) (4) ".

This resubmission provides for a response to the complete response of September 2016.
The CR for this NDA was recommended because FDA Inspectors were not able to conduct the inspection of Lohmann Therapy Systems, the manufacturing facilities for the drug product. The Facility was not ready for inspection. With this resubmission, the Lohmann facilities were ready for inspection, and Office of Facilities within OPQ recommend this facility as adequate.

Further this resubmission provides for the addition of the new facility, Atavis Laboratories, UT, Inc in Salt Lake City.

The drug substance, Buprenorphine HCl remains adequate with a retest period of (b) (4) months when stored at (b) (4)°C. The second drug substance, Naloxone HCl dihydrate, is also adequate with a retest period of (b) (4) months when stored at (b) (4)°C.

4. Nonclinical Pharmacology/Toxicology

In the time since the previous review cycle, a new guidance, ICH Q3D, Elemental Impurities, was implemented after a three-year grace period. This guidance recommends control of the levels of elemental impurities in new and currently marketed drug products. Upon request, Teva submitted an assessment of elemental impurities demonstrating that no elemental impurities exceeded ICH Q3D permissible daily exposures for an oral product or the control thresholds.

5. Clinical Pharmacology

No new clinical pharmacology information was submitted in this review cycle. The text below is reproduced from the first-cycle CDTL memo for the convenience of the reader.

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}, $AUC_{0\text{-last}}$, 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}, $AUC_{0\text{-last}}$, 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
Cmax (pg/mL)	138	6223	3026	133	6752	3004
Tmax (h)	138	1.25	0.33, 3.00	133	1.25	0.33, 3.00
AUClast (h.pg/mL)	138	57392	22572	133	62350	22410
AUCinf (h.pg/mL)	138	60052	23463	133	65314	23398
T1/2 (h)	138	34.61	9.75	133	36.62	11.46

Note: Tmax 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
Cmax (pg/mL)	137	2983	1673	133	3156	1602
Tmax (h)	137	1.00	0.33,48.00	133	1.00	0.49, 48.00
AUClast (h.pg/mL)	137	94096	39148	133	96584	38942
AUCinf (h.pg/mL)	136	104070	44896	132	107934	48882
T1/2 (h)	136	35.09	16.32	132	37.24	20.72

Note: Tmax 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
Cmax (pg/mL)	138	439	245	133	413	237
Tmax (h)	138	0.75	0.33, 2.00	133	0.75	0.33, 2.50
AUClast (h.pg/mL)	138	1015	521	133	957	449
AUCinf (h.pg/mL)	138	1046	523	133	985	451
T1/2 (h)	138	6.56	6.16	133	5.85	4.39

Note: Tmax 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
Cmax (ng/mL)	138	55.6	24.0	133	54.3	23.0
Tmax (h)	138	0.75	0.33, 6.03	133	0.75	0.33, 16.00
AUClast (h.ng/mL)	138	108.2	37.3	133	107.4	38.5
AUCinf (h.ng/mL)	138	111.9	37.7	132	111.0	38.8
T1/2 (h)	138	7.90	3.82	132	8.06	4.33

Note: Tmax 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
Cmax (pg/mL)	5424	6055	89.58	83.98	95.56
AUClast (h.pg/mL)	51945	58222	89.22	84.37	94.35
AUCinf (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
Cmax (pg/mL)	364.2	353.5	103.02	95.80	110.78
AUClast (h.pg/mL)	877.7	869.8	100.91	95.28	106.87
AUCinf (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_{max} 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.

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

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

8. Safety

The safety data is based on the PK studies reviewed in the previous submission which were conducted in healthy volunteers under naltrexone blockade. No new safety concerns were identified.

In summary, 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 Applicant's Module 2 Clinical Overview.

System organ class Preferred term	Study 3007599 (N=80)			Study 4001650 (N=24)[a]				Study 4001651 (N=24) [a]			
	Predose[b] (N=80) n (%)	TEVA (N=79) n (%)	SUBOX (N=79) n (%)	Predose[b] (N=24) n (%)	COLD (N=23) n (%)	HOT (N=23) n (%)	Rm Temp (N=22) n (%)	Predose[b] (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.	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.	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)

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

- 30759: 46 subjects had RR <10, no PO2<90
- 4001650: 19 subjects had RR < 10, 1 had PO2<90 but only pre-dose
- 4001651: 14 subjects had RR<10, no PO2<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.

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

This application does not trigger the requirements of the Pediatric Research Equity Act (PREA) and no pediatric studies were required.

11. Other Relevant Regulatory Issues

11.1 Exclusivity or Patent Issues

Indivior had filed a patent infringement case during first cycle. The 30-month stay expired on August 11, 2018.

11.3 Financial Disclosures

Financial disclosures were reviewed and identified no concerns.

11.4 OSI Inspection

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

11.4 Cardiac Conduction Effects

Based on a signal identified in a study of transdermal buprenorphine at analgesic doses (substantially lower than doses used to treat opioid dependence), companies marketing buprenorphine products for MAT have been issued post-marketing requirements to evaluate the effects of buprenorphine on cardiac repolarization at doses used in opioid dependence treatment.

Currently, the mechanism underlying buprenorphine-induced QT prolongation has not been fully elucidated. Patch clamp electrophysiological studies being conducted at the FDA preliminarily suggest that buprenorphine and its major active metabolite norbuprenorphine do not affect major cardiac ion channels in cardiac cells at clinically relevant concentrations. This suggests that QT prolongation caused by buprenorphine and/or norbuprenorphine is not caused

by the most common mechanism mediating drug-induced torsade de pointes (i.e., direct ion channel block).

Clinical ECGs are still recommended in drug development programs to characterize the dose-/concentration-effect of buprenorphine products on the QTc interval. After several years of exploring options, the Division now believes that a conventional thorough QT study as defined in ICH E14 is not feasible for doses of buprenorphine used in the treatment of opioid dependence. Such studies cannot be done in healthy volunteers who would not tolerate the doses needed, and the crossover design in such a study would repeated tapering and titration of patients, which poses both practical and ethical concerns.

Teva will be required to perform a QT study using alternative designs according to ICH E14 Q&A 6.1, in patients who are actively taking buprenorphine in the clinical setting.

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.

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

- Buprenorphine and Naloxone Sublingual Film is replaced with the proposed proprietary name Cassipa sublingual film.

- 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 to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms. CASSIPA comes in a single dose and cannot be adjusted.
  >
  > [redacted] (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.

- In the Dosage and Administration section , the following is added based on the label for the reference product:

  > There is no maximum recommended duration of maintenance treatment. Patients may require treatment indefinitely and should continue for as long as patients are benefiting and the use of (b) (4) contributes to the intended treatment goals.

- Under Discontinuing Treatment the following is added to be consistent with the reference product.

  > Advise patients of the potential to relapse to illicit drug use following discontinuation of opioid agonist/partial agonist medication-assisted treatment. Managing risks from concomitant use of benzodiazepines or other CNS depressants is updated to conform with the reference product label.

- The overall data in pharmacokinetic study is added to replace the PK after the first dose.
- New required information about 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 and the reference product label 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) .

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. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

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, and Teva has agreed to join the shared REMS.

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

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following post-marketing study will be required:

Conduct a QT study using alternative designs as described in ICH E14 Q&A 6.1 in patients who are initiating treatment with buprenorphine/naloxone in the clinical setting, across the therapeutic dose range. Placebo and positive controls are not necessary. Base the timing of the ECG collection on the known pharmacokinetic properties of buprenorphine/naloxone and include ECGs collected at baseline, after the first dose and at steady state. Conduct this study in the inpatient setting and collect time-match pharmacokinetic samples so that the data can be analyzed using concentration-QTc analysis. The assessment must include an evaluation of any potential delayed effects.

Draft Protocol: March 2019
Final Protocol: September 2019
Study Completion: September 2020
Final Report: December 2020

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/

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09/06/2018

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09/06/2018

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09/07/2018