CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208042Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208042
Supporting document/s:	SDN 16 (eCTD 0014; Resubmission: Response to CR); SDN 29 (Elemental Impurities)
Applicant's letter date:	3/8/2018; 8/29/2018
CDER stamp date:	3/8/2018; 8/29/2018
Product:	CASSIPA (Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg)
Indication:	Maintenance treatment of opioid dependence
Applicant:	Teva Pharmaceuticals
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Elizabeth A. Bolan, PhD
Supervisor/Team Leader:	R. Daniel Mellon, PhD
Division Director:	Sharon Hertz, MD
Project Manager:	Swati Patwardhan

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of 208042 are owned by Teva or are data for which Teva has obtained a written right of reference.
Any information or data necessary for approval of 208042 that Teva does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 208042.

1 Executive Summary

1.1 Introduction

On November 30, 2015, Teva submitted NDA 208042 for Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg, a sublingual film formulation containing buprenorphine hydrochloride (BUP) and naloxone hydrochloride (NLX) in a fixed 4:1 ratio. The NDA was submitted as a 505(b)(2) application relying in part on the Agency's previous finding of safety and efficacy of Suboxone Sublinqual Film (NDA 22410). A Complete Response (CR) was issued by the Division in September of 2016 with a CMC deficiency regarding the inability to conduct a routine inspection of the drug product manufacturing site because the site was not ready for inspection. No other disciplines, including pharmacology toxicology, had deficiencies that would preclude approval at that time. Teva submitted a complete response to the deficiency letter on March 8, 2018. The application contained a literature review since the last submission date.

1.2 Brief Discussion of Nonclinical Findings

There were no nonclinical deficiencies in the complete response letter issued in 2016.

Since the original action in 2016, ICH Q3D, *Elemental Impurities*, was implemented after a three-year grace period. This guidance recommends control the levels of elemental impurities in new and currently marketed drug products. The end of the grace period for implementation of this guidance was technically three years from the data of ICH Publication or December 15, 2017. USP Chapters <232> and <233> which are also currently official discuss the same topic, are aligned with ICH Q3D, and became official August 1, 2017. The FDA issued a guidance noting that January 1, 2018 was the implementation date for the control of elemental impurities in new or existing drug products. TEVA did not address ICH Q3D or the USP minimal requirements in their initial resubmission. However, upon request, TEVA submitted an assessment of elemental impurities that included an analysis of the manufacturing process and raw materials and elemental impurity screening of three lots of the drug product. Expired lots were selected for testing as this was considered to be the worst-case scenario for elemental impurities from packaging materials. No elemental impurities exceeded ICH Q3D permissible daily exposures for an oral product or the control thresholds.

Although of academic interest, the literature submitted did not identify new toxicity studies that impact the current labeling.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 208042 be approved.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the changes proposed by the reviewer and the rationale for the proposed changes based upon the revised referenced Suboxone Sublingual Film labeling. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in red (additions) or strikeout font.

Table 1. Proposed label for CASSIPA (buprenorphine and naloxone sublingual film 16 mg/4 mg)

Applicant's proposed labeling	*Reviewer's proposed changes*	*Rationale for changes*
HIGHLIGHTS OF PRESCRIBING INFORMATION **INDICATIONS AND USAGE** CASSIPA (b) (4) indicated for the maintenance treatment of opioid dependence.	**HIGHLIGHTS OF PRESCRIBING INFORMATION** **INDICATIONS AND USAGE** CASSIPA (b) (4) film contains buprenorphine, a partial-opioid agonist, and naloxone, an opioid antagonist, and is indicated for (b) (4) of opioid dependence.	The Highlights section must include the appropriate FDA Established Pharmacological Classes for BUP and NLX.
USE IN SPECIFIC POPULATIONS	**USE IN SPECIFIC POPULATIONS**	The bullet: "• Pregnancy: May cause fetal harm. (8.1)" which is included in BUP products indicated for pain is not included in products indicated for OUD per the risk/benefit assessment made by the Division.
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Risk Summary Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant and higher	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** *Risk Summary* Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant and higher	The Risk Summary has been updated to reflect the referenced product,

doses. Embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 6-and 0.3-times, respectively, the human sublingual dose of 16 mg/day of buprenorphine. Pre-and postnatal development studies in rats demonstrated increased neonatal deaths at 0.3-times and above and dystocia at approximately 3-times the human sublingual dose of 16 mg/day of buprenorphine. No clear teratogenic effects were seen when buprenorphine was administered during organogenesis with a range of doses equivalent to or greater than the human sublingual dose of 16 mg/day of buprenorphine. However, increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 0.6-and approximately equal to the the human sublingual dose of 16 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalus and omphalocele were also observed but these findings were not clearly treatment-related.	doses. Embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 6 and 0.3 times, respectively, the human sublingual dose of 16 mg/day of buprenorphine. Pre- and postnatal development studies in rats demonstrated increased neonatal deaths at 0.3 times and above and dystocia at approximately 3 times the human sublingual dose of 16 mg/day of buprenorphine. No clear teratogenic effects were seen when buprenorphine was administered during organogenesis with a range of doses equivalent to or greater than the human sublingual dose of 16 mg/day of buprenorphine. However, increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 0.6 times and approximately equal to the ~~the~~ human sublingual dose of 16 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalus and omphalocele were also observed but these findings were not clearly treatment-related *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.	Suboxone SL Film. Minor copy edits were made to the Risk Summary. Note: only the nonclinical section of the Risk Summary is presented. MHT will review the clinical information in the label. Reference to the Data section was added per PLLR.
Animal Data The exposure margins listed below are based on body surface area comparisons (mg/m^2) to the human sublingual dose of 16 mg buprenorphine via (b) (4) [redacted].	*Animal Data* The exposure margins listed below are based on body surface area comparisons (mg/m^2) to the human sublingual dose of 16 mg buprenorphine via CASSIPA (b) (4) [redacted].	The trade name of the product was added.

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM; 3:2) administration of mixtures of buprenorphine and naloxone during the period of organogenesis. Following oral administration to rats, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day (estimated exposure approximately 150 times the human sublingual dose of 16 mg) in the presence of maternal toxicity (mortality). Following oral administration to rabbits, no teratogenic effects wre observed at buprenorphine doses up to 40 mg/kg/day (estimated exposure approximately 50 times the human sublingual dose of 16 mg) in the absence of clear maternal toxicity. No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the human sublingual dose of 16 mg). Maternal toxicity resulting in mortality was noted in these studies in both rats and rabbits. Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Maternal toxicity was seen in the high-dose group but not at the lower doses where the findings were observed. Following oral administration of	Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM, 3:2) administration of mixtures of buprenorphine and naloxone during the period of organogenesis. Following oral administration to rats, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day (estimated exposure approximately 150 times the human sublingual dose of 16 mg) in the presence of maternal toxicity (mortality). Following oral administration to rabbits, no teratogenic effects were observed at buprenorphine doses up to 40 mg/kg/day (estimated exposure approximately 50 times the human sublingual dose of 16 mg) in the absence of clear maternal toxicity. No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the human sublingual dose of 16 mg). Maternal toxicity resulting in mortality was noted in these studies in both rats and rabbits. Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Maternal toxicity was seen in the high-dose group but not at the lower doses where the findings were observed. Following oral administration of	Minor copy edits were made to this section.

buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the human sublingual dose of 16 mg). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.	buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the human sublingual dose of 16 mg). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.	
Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the human sublingual dose of 16 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the human sublingual dose of 16 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the human sublingual dose of 16 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the human (b) (4) sublingual dose of 16 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the	Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the human sublingual dose of 16 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the human sublingual dose of 16 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the human sublingual dose of 16 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the human (b) (4) sublingual dose of 16 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the	This section is acceptable.

human sublingual dose of 16 mg), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the human (b) (4) sublingual dose of 16 mg) in the absence of maternal toxicity or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the human sublingual dose of 16 mg) were not statistically significant.	human sublingual dose of 16 mg), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the human (b) (4) sublingual dose of 16 mg) in the absence of maternal toxicity or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the human sublingual dose of 16 mg) were not statistically significant.	
In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the human (b) (4) sublingual dose of 16 mg). No maternal toxicity was noted at doses causing post-implantation loss in this study.	In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the human (b) (4) sublingual dose of 16 mg). No maternal toxicity was noted at doses causing post-implantation loss in this study.	This section is acceptable.
Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine from Gestation Day 14 through Lactation Day 21 at 5 mg/kg/day (approximately 3 times the human sublingual dose of 16 mg).	Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine from Gestation Day 14 through Lactation Day 21 at 5 mg/kg/day (approximately 3 times the human sublingual dose of 16 mg).	This section is acceptable.
Fertility, pre-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the human (b) (4) sublingual dose 16 mg), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the human sublingual dose of 16 mg), and after SC	Fertility, pre-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the human (b) (4) sublingual dose 16 mg), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the human sublingual dose of 16 mg), and after SC	This section is acceptable.

doses of 0.1 mg/kg/day and up (approximately 0.06 times the human sublingual dose of 16 mg). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the human sublingual dose of 16 mg).	doses of 0.1 mg/kg/day and up (approximately 0.06 times the human sublingual dose of 16 mg). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the human sublingual dose of 16 mg).	
8.3 Females and Males of Reproductive Potential Infertility Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2), and Nonclinical Toxicology (13.1)]*.	**8.3 Females and Males of Reproductive Potential** Infertility Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2), and Nonclinical Toxicology (13.1)]*.	This section is acceptable.
12.1 Mechanism of Action CASSIPA (b) (4) contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.	12.1 Mechanism of Action CASSIPA (b) (4) contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.	This section is acceptable.
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** ***Carcinogenicity:*** Carcinogenicity data on CASSIPA (b) (4) are not available.	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** ***Carcinogenicity:*** Carcinogenicity data on CASSIPA (b) (4) are not available.	The word "recommended" was deleted by the reviewer because the 16 mg dose is

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted. Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86 week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).	A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the ~~recommended~~ human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted. Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the ~~recommended~~ human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86 week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the ~~recommended~~ human daily sublingual dose of 16 mg on a mg/m^2 basis).	not technically “recommended”.
Mutagenicity: The 4:1 combination of buprenorphine and naloxone was	***Mutagenicity:*** The 4:1 combination of buprenorphine and naloxone was	This section is acceptable.

not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli.* The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat. Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.	not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an in vitro cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat. Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.	
Impairment of Fertility: **Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28**	***Impairment of Fertility:*** **Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28**	"Recommended" was deleted by the reviewer because the 16 mg dose is not technically "recommended". "Daily" was deleted

times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) had no adverse effect on fertility.	**times the ~~recommended~~ human ~~daily~~ sublingual dose of 16 mg on a mg/m^2 basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the ~~recommended~~ human ~~daily~~ sublingual dose of 16 mg on a mg/m^2 basis) had no adverse effect on fertility.**	to be consistent with the Suboxone SL Film label.

Elemental Impurities

Three lots of drug product, all expired, were tested for elemental impurities. The use of expired lots is acceptable because this represents the worst-case scenario for elemental impurities from the container closure and elemental impurities do not degrade over time. The maximum daily dose used for this analysis was 16 mg, because this is the only dose for this drug product (the maximum daily dose for Suboxone Film is 24 mg; however, that product contains several dosage forms). The table below presents the results of the analysis.

Table 2: Elemental Impurity Analysis

Table 2: Permitted Daily Exposures & Elemental Impurities based on ICP-MS Screening for Drug Product Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg

Element	Oral PDE (µg/day)	Maximum Permitted Conc. (µg/g)	Control Threshold Conc. (µg/g)	Quantitation Limit (µg/g) (QL)	Results (µg/g)		
					Lot 9902493	Lot 9902543	Lot 9902593
Cd	5			(b) (4)	<QL	<QL	<QL
Pb	5				<QL	<QL	<QL
As	15				<QL	<QL	<QL
Hg	30				<QL	<QL	<QL
Co	50				<QL	<QL	<QL
V	100				<QL	<QL	<QL
Ni	200				<QL	<QL	<QL
Tl	8				<QL	<QL	<QL
Au	100				<QL	<QL	<QL
Pd	100				<QL	<QL	<QL
Ir	100				<QL	<QL	<QL
Os	100				<QL	<QL	<QL
Rh	100				<QL	<QL	<QL
Ru	100				<QL	<QL	<QL
Se	150				<QL	<QL	<QL
Ag	150				<QL	<QL	<QL
Pt	100				<QL	<QL	<QL
Li	550				<QL	<QL	<QL
Sb	1200				<QL	<QL	<QL
Ba	1400				<QL	<QL	<QL
Mo	3000				<QL	<QL	<QL
Cu	3000				<QL	<QL	<QL
Sn	6000				<QL	<QL	<QL
Cr	11000				<QL	<QL	<QL

As noted in the table above, there were no elemental impurities above the permissible day exposures (PDEs) for oral predicts as listed in ICH Q3D. Likewise, no elemental impurity reached the control threshold (1/3 the PDE).

In their analysis of the manufacturing process, the Applicant notes that the only element added during manufacturing is (b) (4), which is added as a (b) (4) However, ATSDR estimates that adult humans consume up to (b) (4) mg of (b) (4) in the diet per day. Further, (b) (4). As such, the small levels of (b) (4) potentially present in the drug product do not present any safety concerns.

Literature Review

The Applicant submitted a comprehensive review of the buprenorphine and naloxone literature from November 30, 2015 through November 10, 2017. Thirty-seven publications and abstracts were identified. A search by this reviewer did not identify additional relevant publications. Although interesting from a scientific perspective, the publications do not affect the approval recommendation or the labeling of this product. One abstract was with a pilot study in rats using a novel model of neonatal abstinence syndrome (NAS) is summarized below.

A pilot study in rats described in an abstract from the 2017 FASEB meeting suggests a role for NBUP as a cause of NAS in neonates born to buprenorphine-treated mothers. The used a novel rat model of NAS which exposes the fetuses to opioids throughout development using an implanted subcutaneous minipump in the dam. After delivery, pups were administered naltrexone in order to precipitate withdrawal. Pups exposed to NBUP showed significantly more signs of withdrawal than control pups. These preliminary data show that NBUP can induce dependence and a withdrawal syndrome in pups after in utero exposure (Brents, et al 2017). No comparison was made to BUP in the study.

REFERENCES

Brents KL, Caperton CO, Patton AL, Owens SM, Moran JH, Stowe JN, Fantegrossi WE (2017) FASEB Journal 31 Suppl. 1: 985.13.

1 (b) (4)

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/

RICHARD D MELLON on behalf of ELIZABETH BOLAN
08/30/2018

GRACE S LEE
08/30/2018

RICHARD D MELLON
08/30/2018
I concur.

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208042
Supporting document/s:	EDR eCTD 0003 (SDN 4; Resubmission after refusal to file)
Applicant's letter date:	Submit date: November 30, 2015
CDER stamp date:	Received date: November 30, 2015
Product:	Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg
Indication:	Maintenance treatment of opioid dependence
Applicant:	Teva Pharmaceuticals
Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Reviewer:	Elizabeth A. Bolan, PhD
Supervisor/Team Leader:	R. Daniel Mellon, PhD
Division Director:	Sharon Hertz, MD
Project Manager:	Matthew Sullivan

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1 Executive Summary

1.1 Introduction

Teva has submitted NDA 208042 for Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg, a sublingual film formulation containing buprenorphine hydrochloride (BUP) and naloxone hydrochloride (NLX) in a fixed 4:1 ratio. The product is planned to be available in one strength of 16 mg/4 mg BUP/NLX, respectively. The indication sought by the Applicant is maintenance treatment of opioid dependence. The Applicant is submitting NDA 208042 via the 505(b)(2) regulatory pathway with Suboxone Sublingual Film (NDA 22410) as the referenced product. The Applicant is relying on the Agency's findings of safety and the pharmacology, pharmacokinetics, and toxicology information in the label of Suboxone. 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, BUP and NLX.

1.2 Brief Discussion of Nonclinical Findings

No new studies were required or submitted for NDA 208042.

1.3 Recommendations

1.3.1 Approvability

The recommendation from pharmacology/toxicology is that NDA 208042 be approved with no post-marketing studies.

1.3.2 Additional Non Clinical Recommendations

There are no nonclinical safety issues unique to this product relevant to clinical use for NDA 208042.

1.3.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the changes proposed by the reviewer and the rationale for the proposed changes based upon the recently revised Suboxone Sublingual Film labeling to be in compliance with PLLR labeling requirements. For the final version of the label, please refer to the Approval Letter. Note: The recommended changes from the proposed labeling are in red (additions) or strikeout font.

Table 1. Proposed label for Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg

Applicant's proposed labeling	***Reviewer's proposed changes***	***Rationale for changes***
INDICATIONS AND USAGE	**INDICATIONS AND USAGE**	The Highlights

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

2 Drug Information

Drug: Buprenorphine Hydrochloride

CAS Registry Number: 53152-21-9

Generic Name: Buprenorphine Hydrochloride

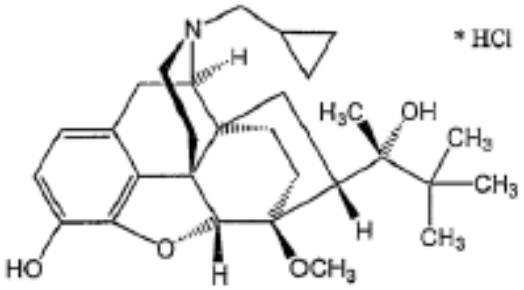
Code Name: N/A

Chemical Name: (2S)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α, 14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol, hydrochloride

Molecular Formula/Molecular Weight: $C_{29}H_{41}NO_4 \cdot HCl$; MW= 504.1 g/mol

Structure:

Figure 1. Structure of buprenorphine hydrochloride



Pharmacologic Class: Partial opioid agonist (FDA Established Pharmacologic Class)

Drug: Naloxone hydrochloride

CAS Registry Number: 51481-60-8

Generic Name: Naloxone hydrochloride

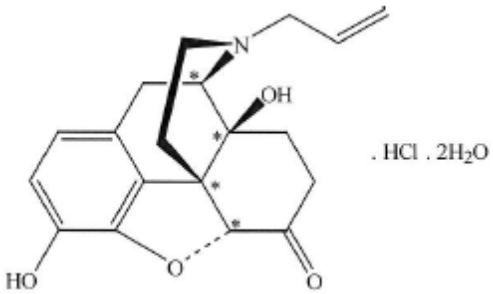
Code Name: N/A

Chemical Name: 4,5α-Epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride

Molecular Formula/Molecular Weight: $C_{19}H_{21}NO_4 \bullet HCl$; MW 399.9 g/mol

Structure:

Figure 2. Structure of naloxone hydrochloride



Pharmacologic class: Opioid antagonist (FDA Established Pharmacologic Class)

Relevant INDs, NDAs, BLAs and DMFs

Table 2. Relevant INDs, NDAs and DMFs

IND/NDA/DMF	*Drug/compound*	*Sponsor*	*Division/Office*	*status*
IND 118625	Buprenorphine and Naloxone	Teva	DAAAP	active
NDA 22410	Suboxone SL Film (referenced drug)	Indivior	DAAAP	approved
DMF 16419	Buprenorphine HCl	Teva Czech Industries	ONDQA	adequate
DMF (b) (4)	Naloxone HCl	(b) (4)	ONDQA	adequate

Drug Formulation

The Applicant is submitting Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg, a sublingual film formulation containing buprenorphine hydrochloride (BUP) and naloxone hydrochloride (NLX) in a fixed 4:1 ratio. The product is planned to be available in one strength of 16 mg/4 mg BUP/NLX (free bases), respectively. Since the product will share the label with the referenced product Suboxone SL Film, the statement "(b) (4) will appear in the label. (b) (4) Since this NDA is for only one strength of 16 mg/4 mg BUP/NLX, the maximum a patient should consume would be one film. The acceptable levels of excipients will be calculated for the consumption of one film. All excipients can be found in drug products approved for chronic use at equal or greater levels and therefore do not pose any unique toxicological concerns (Table 3).

Table 3. Quantitative excipient composition of Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg

#	Ingredient	Function	16 mg/4 mg	
			mg/Film	% w/w
(b) (4)	Buprenorphine Hydrochloride, USP	Active	17.25	(b) (4)
	Naloxone Hydrochloride Dihydrate, USP	Active	4.886	
	Polyethylene Oxide, NF (b) (4)		(b) (4)	
	Maltitol, NF (b) (4)			
	Lemon-Lime Flavor (b) (4)			
	Anhydrous Citric Acid, USP (b) (4)			
	Povidone, USP (b) (4)			
	(b) (4)			
	Acesulfame Potassium Salt, NF (b) (4)			
	Sodium Phosphate, Dibasic, Anhydrous, USP			
	FD&C Yellow #6 (b) (4)			
	Butylated Hydroxyanisole, NF (b) (4)			
	(b) (4)			
	(b) (4) Shellac, USP			
	Propylene Glycol, USP			
	FD&C Blue No.1 (b) (4)			
	(b) (4)			
	Total Weight:		**92.13**	**100**

(b) (4)

(b) (4)

2.4 Comments on Novel Excipients

Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg does not contain any novel excipients.

2.5 Comments on Impurities/Degradants of Concern

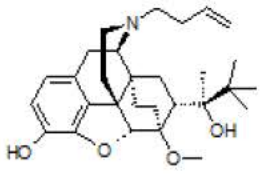
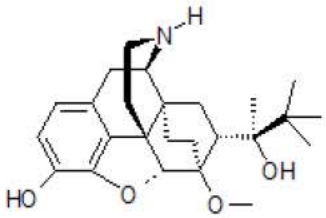
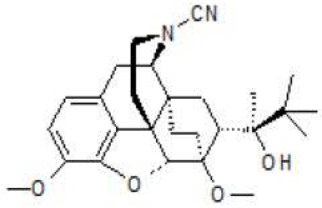
Impurities in the buprenorphine drug substance

The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for a maximum daily dose (MDD) of ≤ 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant has set the specifications for impurities in the buprenorphine drug substance obtained from Teva Czech Industries (DMF 16419) at NMT (b) (4) (Table 4) and no qualification will be necessary. The specifications for the buprenorphine drug substance impurities/degradants are acceptable from a pharmacology/toxicology perspective.

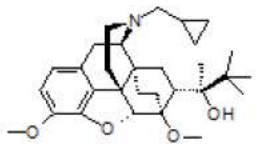
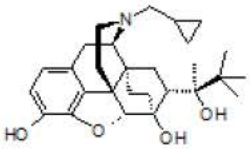
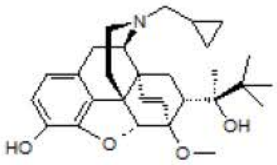
Table 4. Acceptance criteria specifications for the buprenorphine drug substance

Impurity	***Specification***	***Acceptable?***
3-butenyl-DH-nornorthevinol (USP Related Compound A; EP Impurity A)	NMT (b) (4) %	Yes
Norbuprenorphine (EP Impurity B)	NMT %	Yes
Dihydrocyanothevinol (EP Impurity C)	NMT %	Yes
3-methylbuprenorphine (3-*O*-methylbuprenorphine) (EP Impurity D)	NMT %	Yes
6-demethylbuprenorphine 6-*O*-desmethylbuprenorphine (EP Impurity E)	NMT %	Yes
Didehydrobuprenorphine (EP Impurity J)	NMT %	Yes
(b) (4)	NMT %	Yes

Table 5. Buprenorphine HCl-related impurities (table reproduced from NDA 208042)

IUPAC Chemical Name	Code #	Chemical Structure	Process/Degradation Impurity	Source/Mechanism
(6R,7R,14S)-17-(But-3-enyl)-7,8-dihydro-7-[(1S)-1-hydroxy-1,2,2-trimethylpropyl]-6-Omethyl-6,14-ethano-17-normorphine	3-butenyl-DH-nomorthevinol (USP Related Compound A) (EP Impurity A[3])		(b) (4)	
(6R,7R,14S)-7,8-Dihydro-7-[(1S)-1-hydroxy-1,2,2-trimethylpropyl]-6-O-methyl-6,14-ethano-17-normorphine	Dihydronomorthevinol (Norbuprenorphine) (EP Impurity B[4])			
(6R,7R,14S)-17-Cyano-7,8-dihydro-7-[(1S)-1-hydroxy-1,2,2-trimethylpropyl]-3,6-O-dimethyl-6,14-ethano-17-normorphine	Dihydrocyanothevinol (EP Impurity C[5])			

(b) (4)

(6R,7R,14S)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1S)-1-hydroxy-1,2,2-trimethylpropyl]-3,6-O-dimethyl-6,14-ethano-17-normorphine	3-methylbuprenorphine (3-*O*-methylbuprenorphine) (EP Impurity D[6])	
(6R,7R,14S)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-ethano-17-normorphine	6-demethylbuprenorphine 6-*O*-desmethylbuprenorphine (EP Impurity E[7])	
(6R,7R,14S)-17-Cyclopropylmethyl-7,8-dihydro-7-[(1S)-1-hydroxy-1,2,2-trimethylpropyl]-6-Omethyl-6,14-etheno-17-normorphine	Didehydrobuprenorphine (EP Impurity J[8])	

(b) (4)

[3] (2S)-2-[17-(but-3-enyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α, 14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol
[4] (2S)-2-(4,5α-epoxy-3-hydroxy-6-methoxy-6α, 14-ethano-14α-morphinan-7α-yl)-3,3-dimethylbutan-2-ol
[5] 4,5α-epoxy-7α-[(1S)-1-hydroxy-1,2,2-trimethylpropyl]-3,6-dimethoxy-6α,14-ethano-14α-morphinan-17-carbonitrile

[6] (2S)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dimethoxy-6α, 14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol
[7] (2S)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol
[8] (2S)-2-[17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α, 14-etheno-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol

Table 6. Proposed limits of residual solvents for the buprenorphine drug substance

Solvent	***Proposed Specification***	***ICH Qualification Thresholds or Limits***	***Comments***
(b) (4)			

Impurities in the naloxone drug substance

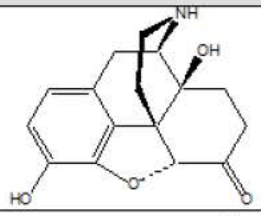
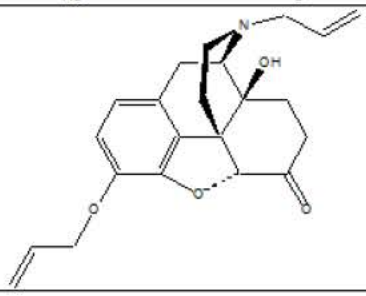
The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for an MDD of ≤ 2 g/day is 0.15% or 1 mg/day intake, whichever is lower. The Applicant has set the specifications for impurities in the naloxone drug substance obtained from (b) (4) (DMF (b) (4)) at or below (b) (4)% (Table 7). The NLX drug substance also contains (b) (4), an impurity with a structural alert for mutagenicity. The current acceptable threshold for known genotoxic impurities is NMT 1.5 mcg/day. The Applicant has set the specification of (b) (4) at (b) (4)%. This specification is within the drug substance specification for (b) (4) of the referenced product which has been deemed acceptable by the Agency. The specification of (b) (4)% for (b) (4) in the drug substance is acceptable. Additionally, at a MDD of 4 mg for NLX in this product, the (b) (4)% specification would yield (b) (4) mcg of (b) (4). This is below the 1.5 mcg/day threshold for genotoxic impurities currently accepted by the Agency. The specifications for all of the NLX drug substance impurities/degradants are acceptable from a pharmacology/toxicology perspective.

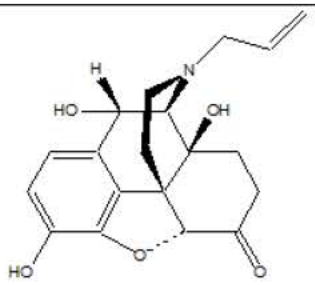
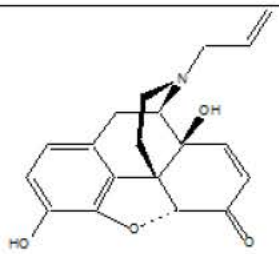
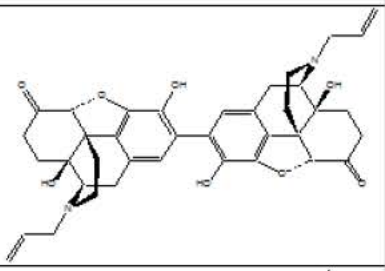
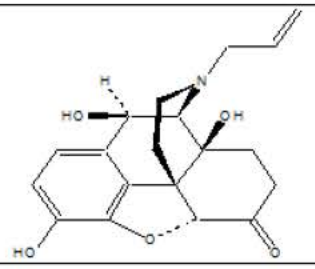
Table 7. Acceptance criteria specifications for the naloxone drug substance

Impurity	***Specification***	***Acceptable?***
Noroxymorphone (EP Impurity A)	NMT (b) (4)%	Yes
3-O-Allylnaloxone (EP Impurity B)	NMT %	Yes
10-α-Hydroxynaloxone (EP Impurity C)	NMT %	Yes
7,8-Didehydronaloxone (EP Impurity D)*	NMT (b) (4)%	Yes
2,2'-Bisnaloxone (EP Impurity E)	NMT (b) (4)%	Yes
10-ß-Hydroxynaloxone (EP Impurity F)	NMT %	Yes

*structural alert for mutagenicity

Table 8. Naloxone HCl dihydrate-related impurities (table reproduced from NDA 208042)

IUPAC Chemical Name	Code #	Chemical Structure	Process/Degradation Impurity	Source/Mechanism
(4R,4aS,7aR,12bS)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7aH)-one	Noroxymorphone (EP/USP Impurity A[10])		(b) (4)	
(4R,4aS,7aR,12bS)-3-allyl-9-(allyloxy)-4a-hydroxy-2,3,4,4a,5,6-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7aH)-one	3-O-allylnaloxone (EP Impurity B[12])			

			(b) (4)
(4R,4aS,7aR,12bS,13S)-3-allyl-4a,9,13-trihydroxy-2,3,4,4a,5,6-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7aH)-one	10-α-Hydroxynaloxone (EP Impurity C[13])		
(4R,4aS,7aR,12bS)-3-allyl-4a,9-dihydroxy-2,3,4,4a-tetrahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7aH)-one	7,8-didehydronaloxone (EP Impurity D[14])		
[2,2'-Bimorphinan]-6,6'-dione, 4,5:4',5'-diepoxy-3,3',14,14'-tetrahydroxy-17,17'-bis(2-propenyl)-, (5α)-(5'α)- (9CI)	2,2'-bisnaloxone (EP Impurity E[15])		
(4R,4aS,7aR,12bS,13R)-3-allyl-4a,9,13-trihydroxy-2,3,4,4a,5,6-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7(7aH)-one	10-ß-Hydroxynaloxone (EP Impurity F[16])		

[10] 4,5α-epoxy-3,14-dihydroxymorphinan-6-one

(b) (4)

[12] 4,5α-epoxy-14-hydroxy-17-(prop-2-enyl)-3-(prop-2-enyloxy)morphinan-6-one

[13] 4,5α-epoxy-3,10α,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one
[14] 7,8-didehydro-4,5α-epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one
[15] 4,5α:4',5'α-diepoxy-3,3',14,14'-tetrahydroxy-17,17'-bis(prop-2-enyl)-2,2'-bimorphinanyl-6,6'-dione
[16] 4,5α-epoxy-3,10β,14-trihydroxy-17-(prop-2-enyl)morphinan-6-one

Table 9. Proposed limits of residual solvents for the naloxone drug substance

Solvent	***Proposed Specification***	***ICH Qualification Thresholds or Limits***	***Comments***
			(b) (4)

Impurities in the drug product

The qualification threshold according to the ICH Q3B(R2) guidelines for impurities/degradants in the drug product for an MDD between 10 mg and 100 mg of BUP administered per day is 0.5% or 200 mcg TDI, whichever is lower. The specifications for the BUP-derived impurity/degradant in the drug product are considered acceptable (Table 10).

The MDD of the NLX portion of this product is <10 mg/day, therefore the qualification threshold according to the ICH Q3B(R2) guidelines is 1.0% or 50 mcg TDI, whichever is lower. The specifications for the NLX-derived impurity/degradant in the drug product are considered acceptable (Table 10).

Table 10. Stability specifications for Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg

Impurity	***Specification***	***Acceptable?***
Buprenorphine-derived		
EP Impurity B	NMT (b) (4) %	Yes
EP Impurity G	NMT (b) (4) %	Yes

Naloxone-derived		
USP/EP Impurity A	NMT (b) (4) %	Yes
EP Impurity C	NMT (b) (4) %	Yes
EP Impurity E	NMT (b) (4) %	Yes
EP Impurity F	NMT (b) (4) %	Yes

2.6 Proposed Clinical Population and Dosing Regimen

The indication sought for Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg is maintenance treatment of opioid dependence. The Applicant plans to market one strength of 16 mg/4 mg BUP/NLX which is intended for a single daily dose. The highest dose available for Suboxone film strip or tablet is 8 mg/2 mg BUP/NLX. To achieve the maximum dose of 16 mg/4 mg BUP/NLX, two strips/tablets are utilized. This product provides the 16 mg/4 mg dose in a single film strip. Teva has two ANDAs currently under review for the lower strengths with Suboxone as the referenced listed drug. The 16 mg/4 mg is a new strength, therefore and NDA was filed.

2.7 Regulatory Background

The Applicant submitted NDA 208042 via the 505(b)(2) pathway with Suboxone SL Film (NDA 22410) as the referenced product. In July 2013, written responses were provided to the Applicant in lieu of a PIND meeting (PIND 118625) was held with the Applicant in July of 2013. No specific pharmacology toxicology questions were posed but the Division provided guidance regarding acceptable levels of impurities, impurities with structural alerts containing (b) (4) and excipients. In May of 2014 the Division provided written responses in lieu of a meeting. The Division answered a question regarding the levels of excipients used in the formulation. It was communicated to the Applicant that the excipients, with the exception of (b) (4) Lemon-Lime (b) (4) flavoring, appeared not to require additional toxicologic qualification. The referenced DMF for the flavoring will be reviewed with the NDA or sooner if resources permit. Further guidance was provided to the Applicant regarding the appropriate exposure margins for the product labeling. The boilerplate pre-NDA comments were also given to the Applicant.

3 Studies Submitted

No nonclinical studies were required or submitted with NDA 208042.

4 Pharmacology

4.1 Primary Pharmacology

Buprenorphine is a synthetic opioid agonist that is 10-20 times more potent than morphine with a very long duration of action. It acts as a partial mu opioid receptor agonist and a kappa opioid receptor antagonist. Naloxone is a nonspecific opioid receptor antagonist. At low doses BUP produces sufficient agonist effect to enable opioid-addicted individuals to discontinue the misuse of opioids without experiencing withdrawal symptoms. The NLX component of the formulation serves to attempt to prevent abuse of the product. Naloxone is rapidly metabolized via the oral and sublingual routes resulting in low bioavailability, however, with parenteral administration, as in an abuse situation, the NLX is bioavailable to block the effects of BUP and induce withdrawal symptoms in an opioid tolerant person.

4.2 Secondary Pharmacology

The secondary pharmacologic effects of a mu opioid agonist such as BUP include dysphoria, euphoria, and sedation.

4.3 Safety Pharmacology

The CNS effects of BUP are well-known and extensive clinical experience exists with both BUP and NLX. No new safety pharmacology studies were conducted for NDA 208042.

5 Pharmacokinetics/ADME/Toxicokinetics

No new PK studies were submitted for NDA 208042. Based on literature, the major metabolic pathway of BUP in human is via N-dealkylation by CYP3A4 to nor-BUP (Kobayashi K, et al., 1998). The bioavailability of the NLX component of this product by the sublingual route is very low. The NLX is included in the formulation in order to deter abuse by parenteral routes.

6 General Toxicology

No general toxicology studies were conducted for NDA 208042.

7 Genetic Toxicology

No genetic toxicology studies were conducted for NDA 208042. Genetic toxicology studies with BUP and the BUP/NLX combination from the label of the referenced product are described in the product label.

8 Carcinogenicity

No carcinogenicity studies were conducted for NDA 208042. Carcinogenicity studies with BUP and the BUP/NLX combination from the label of the referenced product are described in the product label.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were conducted for NDA 208042 but studies using BUP and the BUP/NLX combination from the label of the referenced product are described in the product label. Both BUP and NLX are designated Pregnancy Category C. This product will be designated a Pregnancy Category C.

10 Special Toxicology Studies

No special toxicology studies were conducted.

11 Integrated Summary and Safety Evaluation

No nonclinical studies were required for NDA 208042. Exposures between this product and the referenced product Suboxone were shown to be comparable, therefore, no nonclinical studies with either BUP or NLX were deemed necessary. 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. The risk assessment for this product is no different than the referenced product Suboxone.

Reference List

1. Kobayashi K, Yamamoto T, Chiba K, Tani M, Shimada N, Ishizaki T and Kuroiwa Y (1998) Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metab Dispos* **26**:818-821.

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/s/

ELIZABETH BOLAN
08/19/2016

RICHARD D MELLON
08/19/2016
I concur.