

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204242Orig1s000**

**SUMMARY REVIEW**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

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Summary Review for Regulatory Action

<b>Date</b>	July 3, 2013
<b>From</b>	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	204242
<b>Applicant Name</b>	Orexo AB
<b>Date of Submission</b>	September 5, 2012
<b>PDUFA Goal Date</b>	July 6, 2013
<b>Proprietary Name / Established (USAN) Name</b>	Zubsolv buprenorphine and naloxone sublingual tablets
<b>Dosage Forms / Strength</b>	5.7 mg buprenorphine/1.4 mg naloxone 1.4 mg buprenorphine/0.36 mg naloxone
<b>Proposed Indication</b>	Maintenance treatment of opioid dependence
<b>Action:</b>	Approval

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
CDTL	Celia Winchell, M.D.
Clinical Review	Pamela Horn, M.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D.; R. Daniel Mellon, Ph.D.
ONDQA-CMC/Quality Review	Julia Pinto, Ph.D.; Prasad Peri, Ph.D.
Biopharmaceutics Reviewer	Akm Khairuzzaman, Ph.D.
Clinical Pharmacology Review	Wei Qiu, Ph.D.; Yun Xu, Ph.D.
Pediatric and Maternal Health Staff	Leyla Sahin, M.D.; Melissa Tassinari, Ph.D.; Lynne Yao, M.D.
Project Management	Matthew Sullivan, M.S.
OSE/DMEPA	Vicky Borders-Hemphill, Pharm.D.; Jamie Wilkins Parker, Pharm.D.; Lubna Merchant, Pharm.D.; Carol Holquist, R.Ph.
OSE/DRISK	Jason Bunting, Pharm.D.; Reema Mehta, Pharm.D., MPH
OMP/OMPI/DMPP	Barbara Fuller, R.N., M.S.N.; Nathan Caulk, M.S., B.S.N., R.N.
OSI/ Division of Bioequivalence and GLP Compliance	Young Moon Choi, Ph.D., Sam H. Haidar, Ph.D., R.Ph., William H. Taylor, Ph.D.
OMP/OPDP/DDTCP	L. Shenee' Toombs, Pharm.D.
Controlled Substances Staff	Stephen Sun, M.D.; Michael Klein, Ph.D.

OND=Office of New Drugs  
 OMP: Office of Medical Policy  
 OMPI=Office of Medical Policy Initiative  
 OPDP= Office of Prescription Drug Promotion  
 DMPP = Division of Medical Policy Programs  
 DDTCP: Division of Direct-to-Consumer Promotion  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention  
 DRISK= Division of Risk Management  
 OSI=Office of Scientific Investigations  
 CDTL=Cross Discipline Team Leader  
 ONDQA=Office of New Drug Quality Assessment

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## 1. Introduction

Orexo AB has submitted this NDA in support of the approval of Zubsolv, their new formulation of buprenorphine/naloxone sublingual tablets indicated for the maintenance treatment of opioid dependence. This is a 505(b)(2) application for which the listed application is Suboxone (NDA 020733). Due to differences in bioavailability when compared to Suboxone, the nominal doses are lower for Zubsolv. However, comparative pharmacokinetic (PK) studies have demonstrated that the exposures seen with Zubsolv are bioequivalent to those seen with Suboxone. Zubsolv tablets are only indicated for patients who have already been started in treatment on buprenorphine-only sublingual products.

## 2. Background

The following summary of the background information important to understanding this application has been reproduced from pages 2 to 3 of Dr. Winchell's review:

Buprenorphine is a partial agonist at the  $\mu$ -opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain<sup>1</sup>, two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence<sup>2</sup>, and a sublingual film formulation for opioid dependence<sup>3</sup> and an extended-release transdermal film formulation for pain<sup>4</sup> were approved in 2010.

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the  $\mu$ -receptor. Like methadone, buprenorphine's activity at the  $\mu$ -receptor was expected to relieve patients' urge to use illicit opioids, but like methadone, the long duration of action would allow patients to achieve a steady state, without the alternating highs and lows associated with opioid abuse that impair daily functioning. Additionally, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, further deterring abuse of these substances for buprenorphine-maintained patients.

Due to its partial agonist properties, the euphorogenic effects of buprenorphine are 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. This was expected to limit its attractiveness as a drug of abuse relative to full agonists.

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<sup>1</sup> Buprenex, NDA 18401 Reckitt Benckiser

<sup>2</sup> Subutex (buprenorphine sublingual tablets), NDA 20732 and Suboxone (buprenorphine/naloxone sublingual tablets), NDA 20733, Reckitt Benckiser

<sup>3</sup> Suboxone (buprenorphine naloxone) film, NDA 22410, Reckitt Benckiser

<sup>4</sup> Butrans, NDA 21306

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Because it is 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. This product references the application for Suboxone, NDA 20733 (Reckitt Benckiser), a sublingual tablet formulation of buprenorphine that also contains 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 product was developed under IND 110637. Orexo originally met with the Division in a pre-IND meeting in February, 2011. At that time, they were advised that no clinical efficacy or safety data would be required, provided that the buprenorphine exposure was bioequivalent to the reference product. Regarding naloxone, the Applicant was advised that the naloxone exposure could be lower than the reference product, but that they would need to provide information to show that the product would release sufficient naloxone under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids.

Naloxone is included in this formulation with the intent of providing a measure of abuse deterrence to the product. Since naloxone can precipitate withdrawal in individuals who are physically dependent on full opioid agonists, it is intended to result in precipitated withdrawal in individuals who manipulate the formulation for intravenous injection. While naloxone is only minimally absorbed sublingually or via oral ingestion, when injected intravenously, the quantity available in this formulation is likely to result in some degree of aversive symptoms. However, even with minimal absorption when taken as prescribed, it is recommended that patients transitioning from full opioids be initially treated with buprenorphine-only products. Once the patient has achieved maintenance on one of those products, the combination product can be safely introduced as naloxone competes poorly with buprenorphine at the mu receptor.

It is important to note that buprenorphine, while a Schedule III Controlled Substance and subject to the prescribing regulations supporting the Controlled Substances Act, when used as agonist therapy in the treatment of opioid addiction, it is also subject to an additional set of regulations supporting the Drug Addiction Treatment Act of 2000 (DATA 2000). See Section 11 below for additional information regarding these regulations and their impact on this application.

The Applicant requested a priority review based on their contention that the blister packaging of this product would deter accidental pediatric exposure. The following comments regarding our decision not to grant a priority review have been reproduced from page 5 of Dr. Winchell's review:

...a recent analysis of accidental pediatric exposures to Subutex and Suboxone tablets (which are not in unit-of-use packaging) and Suboxone films (which are) did not definitively establish a role for the unit-of-use packaging. Although it seems intuitively appealing to conclude that blister-packaged products would be less likely to be involved

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in accidental pediatric exposures, it was noted in the recent review that a number of cases involved exposures to fractions of tablets. Many patients use partial tablets, either because they are not following prescriber's directions, or because the prescriber advises dividing the larger (8 mg) tablets into smaller pieces for dose titration. In these circumstances, even a product originally shipped in blister packaging is no longer protected once it is removed from the package and divided by the patient.

### 3. CMC

The following has been reproduced from pages 7 and 8 of Dr. Pinto's second review:

#### A. Recommendation and Conclusion on Approvability

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, has been provided in this NDA submission for the two drug substances. However two deficiencies had been identified during the first review, concerning the analytical methods for determination of Assay of Naloxone HCL in the drug product and the determination of the related substances in the drug product. These deficiencies have been satisfactorily addressed. The Sponsor has agreed to a PMC to revise and validate the organic impurities analytical method. Further, the Office of Compliance has made overall recommendation of adequate for all facilities related to this application. Therefore, from a quality perspective, this NDA is recommended for approval with the PMC stated in the next section.

#### Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable-

Revise and validate the analytical method for organic impurities in the Naloxone API of the drug product accordingly to reflect an accuracy of (b) (4) RSD and intermediate precision of (b) (4) RSD.

#### II. Summary of Chemistry Assessment

##### A. Description of Drug Substance and Drug Product:

There are two drug substances in the drug product. The first, buprenorphine HCL, is referenced to DMF (b) (4) and has been reviewed as Adequate (Rev 1, J. Pinto/B. Bolan, April 2013). Buprenorphine will be stored (b) (4). The Second drug substance, Naloxone HCl dihydrate, is referenced to DMF (b) (4) also reviewed as adequate by M. Pineiro-Sanchez, Chem Review #5, March 2013). A retest period for Naloxone HCl (b) (4) is (b) (4) when stored at 25°C/60% RH. The drug substances are (b) (4) and a (b) (4) particle size is controlled according to USP <429>.

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The drug product is a sublingual tablet in two strengths 1.4mg/0.36mg and 5.7mg/1.4mg. The manufacturing process consists (b) (4)

The inactive ingredients include mannitol, citric acid, sodium citrate (b) (4), microcrystalline cellulose, croscarmellose sodium, sucralose, menthol, silicon dioxide (b) (4) and sodium stearyl fumarate. The RLD for this drug product is Suboxone®, also a sublingual tablet with the same APIs in the same 4:1 ratio. The tablets are packaged in blister packages in sheets of 10 with 3 sheets to one carton. The requested expiry of 18 months for the low strength is supported by real time data. The requested expiry of (b) (4) months for the higher strength is not. Therefore an expiry of 18 months is recommended for both tablet strengths. The Office of Compliance has made an adequate recommendation for all the facilities.

A request for a biowaiver for the lower strength tablet was reviewed and granted by the ONDQA Biopharm reviewer (Akm Khairuzzaman Ph.D.).

The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 18 months is supported.

#### **B. Description of How the drug is intended to be used:**

Zubsolv™ is a Sublingual tablet that delivers a combination of buprenorphine and naloxone for maintenance treatment of opioid dependence. Zubsolv™ sublingual tablets, are easily placed under the tongue, and are rapidly disintegrating tablets with (b) (4). They are available in two strengths used for dose titration: a high strength of 5.7 mg of buprenorphine /1.4 mg naloxone and a low strength of 1.4 mg buprenorphine/ 0.36 mg naloxone. Both tablets are white and are differentiated by shape and debossing on one side of the tablet. The high strength is a round flat-faced radius-edged tablet 7 mm in diameter debossed with 5.7, representing 5.7 mg buprenorphine. The low strength is a triangular shaped (base 7.2 mm, height 6.9 mm) flat-faced, radius-edged tablet debossed with 1.4, representing 1.4 mg buprenorphine.

#### **C. Basis for Approvability Recommendation**

Sufficient CMC information, to assure the identity, strength, purity, and quality of the drug product, is provided in this NDA submission. All previously identified deficiencies have been adequately addressed and the Office of Compliance has recommended all facilities related to this application as Satisfactory.

Therefore, I concur with the review team that there are no outstanding CMC concerns that would preclude approval of this application.

## **4. Nonclinical Pharmacology/Toxicology**

No new nonclinical pharmacology or toxicology data were submitted in this NDA.

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## 5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology and biopharmaceutics data submitted in this application has been reproduced from pages 9 and 10 of Dr. Winchell's review:

### 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

#### Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone doses and 16mg Subutex dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone 4 mg	Suboxone 8 mg	Suboxone 16 mg	Subutex 16 mg
$C_{max}$ , ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC <sub>0-48</sub> , hour.ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

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).

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Renal impairment does not affect buprenorphine PK. The effects of renal failure on naloxone PK are unknown.

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## 5.2 Clinical Pharmacology Findings

The clinical pharmacology review was conducted by Wei Qui, Ph.D., supervised by Yun Xu, Ph.D. Two studies of developmental formulations and two studies of the higher strength of the to-be-marketed formulation were submitted. Orexo requested and received a biowaiver for the lower strength of the to-be-marketed formulation (1.4/0.36 mg) (ONDQA/Biopharm reviewer, Dr. Akm Khairuzzaman.)

Comparative bioavailability of the higher strength of the to-be-marketed formulation (5.7/1.4 mg) and the listed drug Suboxone sublingual tablet (8/2 mg) was studied in Study OX219-003. The dose proportionality of the formulation was evaluated in Study OX219-004.

Dr. Qui's key findings were as follow:

1. Zubsolv 5.7/1.4 mg sublingual tablet exhibited equivalent systemic exposure (C<sub>max</sub>, AUC<sub>t</sub>, and AUC<sub>inf</sub>) to buprenorphine in comparison to the listed drug, Suboxone 8/2 mg sublingual tablet.
2. Zubsolv 5.7/1.4 mg sublingual tablet had equivalent naloxone C<sub>max</sub>, 12% lower naloxone AUC<sub>t</sub>, and 16% lower naloxone AUC<sub>inf</sub> values in comparison to Suboxone 8/2 mg sublingual tablet.
3. The median dissolve time of Zubsolv 5.7/1.4 mg was 5 minutes while the median dissolve time of Suboxone 8/2 mg sublingual tablet was 12.5 minutes.
4. Dose-proportionality was not demonstrated for buprenorphine C<sub>max</sub> and AUC values over the range of 1.4 mg to 11.4 mg. The increases in systemic exposure were slightly less than dose proportional as dose increased from 1.4 to 11.4 mg.
5. Dose-proportionality was demonstrated for naloxone AUC<sub>t</sub> and AUC<sub>inf</sub> over the range of 0.36 mg and 2.8 mg. C<sub>max</sub> values increased in a slightly less than dose proportional fashion.

This degree of departure from dose-proportionality is not a major concern because the drug is generally titrated to effect.

## 5.3 QT assessment

No QT assessment was undertaken in this development program.

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

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I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application.

## 6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

## 7. Clinical/Statistical-Efficacy

There were no new data submitted in regard to the efficacy of the buprenorphine component.

The following summary of the information submitted in support of the efficacy of the naloxone component in causing aversive effects when the product is crushed and injected has been reproduced from pages 11 and 12 of Dr. Winchell's review:

Dr. Stephen Sun, Controlled Substances Staff, reviewed the extraction study, and noted: "[Orexo] provided results from an in vitro extraction study of OX219 [Zubsolv] (Report 10 3299) under the following 8 conditions: (b) (4)

(b) (4) In all conditions at 1, 5, and 10 min time points, the ratio of 4:1 buprenorphine: naloxone was not exceeded suggesting ratio was maintained when dissolved. Buprenorphine does not appear to be preferentially extracted. In vitro extraction studies, conducted in triplicate, showed that (b) (4) naloxone and (b) (4) BUP was released."

The ability of naloxone doses of (b) (4) or lower to produce aversive effects in opioid-dependent patients was supported by published articles identified via PubMed search. Dr. Pamela Horn reviewed these and noted the following:

- 12 clinical studies evaluated withdrawal in persons dependent on full  $\mu$ -agonists (9 on methadone, 1 on morphine, 1 on hydromorphone, and 1 on tramadol) with parenteral doses of (b) (4) mg naloxone
- Of these 12 studies, 10 showed evidence of precipitated withdrawal with (b) (4) mg naloxone. Measures of opioid withdrawal symptoms included the SOWS, WOWS, OOWS and VAS scales.
- Subjects treated with naloxone did not show evidence of precipitated withdrawal in two studies.

Dr. Horn points out that most information on the aversive effects of parenteral doses of naloxone of 0.3 mg and less was established in subjects dependent on methadone. Nine out of ten of the studies that showed evidence of precipitated withdrawal studied methadone.

Methadone-maintained patients may not be representative of all individuals dependent on full agonists. Therefore, the study in morphine-dependent subjects is of particular interest. In this study, opioid-dependent volunteers were titrated to 15, 30, 60, or 120 mg IM morphine per day. Naloxone 0.3 mg IM was sufficient to produce subjective aversive

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effects that were statistically significantly different from placebo as measured on the bad effects and sick VAS, ARCI, and adjective rating scales in subjects on 60 and 120 mg morphine per day. In another study, subjects maintained on 40 mg PO hydromorphone per day (similar to morphine ~50 -60 mg IM per day) did not experience precipitated withdrawal from 0.25 mg IM naloxone.

The study conducted in subjects dependent on morphine indicates that the effects of naloxone in doses of 0.3 mg or less are not unique to methadone and can be expected to generalize to full opioid agonists as a class, provided the level of physical dependence is sufficiently high. The 120 mg IM morphine dose probably more closely approximates doses used by dependent individuals than do the lower maintenance doses studied. Effects were not limited to changes in vital signs or pupillary diameter, which are objective signs of withdrawal which would not be experienced as aversive. Instead, effects were demonstrated on subjective measures, consistent with the objective of producing an aversive experience if the product is misused. However, in some studies, the severity of symptoms was not particularly high. Currently, the Suboxone labeling indicates that a “marked and intense” withdrawal syndrome is “highly likely” to occur if the product is crushed and injected. It is not clear that “marked and intense” is an appropriate description of the symptoms produced by lower doses of naloxone, or that it is “highly likely” to occur.

Additionally, individuals who abuse buprenorphine commonly use less than a full tablet dose. (The discussion provided by the applicant included the assumption that drug abusers would be likely to take more than one tablet’s worth of buprenorphine at a time to obtain higher doses; this does not appear to be consistent with observations about buprenorphine abuse.) These individuals will be exposed to even lower doses of naloxone.

Therefore, it is likely that under some conditions, Zubsolv can be injected without precipitating withdrawal. However, this is known to be the case with the reference product as well. (b) (4)

The labeling should also continue to avoid statements which imply that the naloxone has been shown epidemiologically to have abuse-deterrent effects, and should state (as it currently does) that physicians should be aware that patients and drug abusers can and do abuse buprenorphine/naloxone combinations by the intravenous route.

I concur with the review team that the Applicant has documented that Zubsolv is effective for the proposed indicated use.

## 8. Safety

The following summary of the clinical safety information submitted in this application has been reproduced from pages 12 and 13 of Dr. Winchell’s review:

Because this is not a novel dosage form or route of administration, and the systemic exposure is the same as the reference product, the safety of this product rests primarily on previous Agency findings for Suboxone.

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Local tolerability was evaluated in the clinical pharmacology studies. Because these studies were conducted in healthy volunteers under naltrexone blockade, the systemic adverse event information is not informative.

Overall, there were 233 single dose exposures to the final clinical product in 114 subjects. There were 53 exposures in 53 subjects in Study 003 and 180 exposures in 61 subjects in Study 004. The table below (Dr. Horn's Table 2) summarizes all exposures in the development program.

**Table 1 Exposure by Formulation and Dose**

Study	Formulation / Dose [mg buprenorphine / mg naloxone]								
	OX219-1 6/1.5	OX219-3 4.5/1.125    5.5/1.375		OX219-4 (Final Commercial Product) 1.4/0.36    5.7/1.4    8.5/2.12 <sup>a</sup> 11.4/2.8 <sup>b</sup>				OX219 All	Suboxone <sup>c</sup>
OX219-001	18	-	-	-	-	-	-	18	18
OX219-002	-	23	24	-	-	-	-	47	22
OX219-003	-	-	-	-	53	-	-	53	60
OX219-004 <sup>c</sup>	-	-	-	45	46	45	44	180	-
Total	18	23	24	45	99	45	44	298	100

<sup>a</sup> 8.5/2.12 mg was administered as one tablet of OX219-4, 5.7/1.4 mg + two tablets of OX219-4, 1.4/0.36 mg

<sup>b</sup> 11.4/2.8 mg was administered as two tablets of OX219-4, 5.7/1.4 mg

<sup>c</sup> The 61 subjects enrolled in Study OX219-004 did not participate in each period (13 subjects who participated in Period 1 only were replaced with 13 subjects who participated in Periods 2 and 3, see Appendix 16.2.1.2, CSR OX219-004, Module 5.3.1.1).

Source: Table 3, p. 22, ISS

There were no deaths or serious adverse events in the development program.

The development program mainly consisted of single exposures in naltrexone-blocked subjects and there were no studies with multiple consecutive dosing, leaving little opportunity for premature discontinuation. Subjects in Study 004 (N = 61 ) had exposure to multiple doses separated by a washout period and could have discontinued due to a local tolerability issue after a single dose before moving on to the next dose.

There were no deaths or serious adverse events. There were 14 discontinuations due to 19 adverse events, primarily attributable to naltrexone effects (GI symptoms). None involved adverse events of the oral cavity. No local tolerability concerns emerged from the data.

I concur with the review team that no new or unexpected safety signals have been demonstrated during this development program.

## 9. Advisory Committee Meeting

As this was a simple reformulation of an already approved combination drug product, the application was not presented to an advisory committee.

## 10. Pediatrics

The following summary of the pediatric information in this application has been reproduced from pages 13 and 14 of Dr. Winchell's review:

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Orexo requested a full waiver of the pediatric studies required under the Pediatric Research Equity Act (PREA). The justification provided was based on safety concerns in the neonatal age group, where buprenorphine may be used to treat symptoms of neonatal abstinence syndrome (NAS). Orexo noted that the claimed indication (maintenance treatment of opioid dependence) is not relevant in this population. Opioid dependence is not managed with maintenance treatment in the neonate, but there is increasing research interest in the use of buprenorphine for NAS. However, this product contains naloxone, which serves no purpose in the treatment of neonatal abstinence syndrome and might present a safety concern. Therefore, the Division agreed that a waiver in this age group was appropriate.

Waivers for Ages 5 weeks to 12 years and Age 12 to 16 years were requested on the grounds that studies would be impossible or highly impracticable, due to the low prevalence of opioid abuse and dependence. (b) (4)

For Age 12 to 16, Orexo assessed the prevalence of opioid addiction using the National Survey of Drug Use and Health. The data are shown below, taken from Dr. Horn's review.



## 11. Other Relevant Regulatory Issues

As noted above in Section 2, there are legal and regulatory constraints on buprenorphine prescribing beyond those covered by the CSA. The following

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summary of this issue has been reproduced from pages 4 and 5 of Dr. Winchell's review:

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

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

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

## 12. Labeling

The following comments regarding labeling for use in pregnancy and nursing have been reproduced from page 16 of Dr. Winchell's review:

Dr. Leyla Sahin of the Pediatric and Maternal Health Staff's Maternal Health Team reviewed literature on the use of buprenorphine in pregnancy and nursing. She concluded:

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Since buprenorphine's approval in 2002, there has been an accumulation of published data on neonatal and infant outcomes following the use of buprenorphine in pregnancy and lactation. The medical literature includes a randomized, controlled trial comparing neonatal abstinence syndrome (NAS) outcomes in 58 buprenorphine exposed women vs. 73 methadone exposed women (the MOTHER study), two very small pilot RCTs, several published prospective observational studies, and case series and reports. Thus, new information from published data on the consequences for newborns of use of this product in pregnant women should be added to labeling. The available published data have not shown an increase in malformations, and there does not appear to be a dose response relationship between the maternal buprenorphine dose and the incidence of neonatal abstinence syndrome. Available published data on exposure during lactation have shown that buprenorphine is present in very low levels in breast milk and have not shown adverse reactions in breastfeeding infants.

Based on Dr. Sahin's review, certain portions of labeling were revised to reflect new information and to conform with current recommendations for the sections related to use in pregnancy and nursing.

Dr. Winchell's summary of the other labeling negotiations and changes of importance for this application has been reproduced below from pages 16 and 17 of her review:

The proprietary name, Zubsolv, was found acceptable prior to NDA submission.

Physician labeling was based on the PLR version of the labeling for the reference product, which, in turn, was supported by studies of a formulation that was not ultimately marketed. Therefore, some revisions focused on clearly conveying when the data were drawn from studies of other products. Key differences between the sponsor's proposed labeling and the labeling proposed by the review team include:



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- Language describing the potential for precipitated withdrawal related to naloxone were revised to remove the statement that the symptoms are “(b) (4)” and “(b) (4)” because the studies submitted suggested that the reaction is likely in most, but not all, individuals, and that it may (b) (4).
- In several places, the Applicant proposed language stating that the bioavailability of Zubsolv is (b) (4) that of Suboxone. This is true, and it is important to note that the bioavailability is different, so that patients and prescribers understand that 5.7 mg of Zubsolv corresponds to 8 mg of Suboxone. However, it was anticipated that the language noting “(b) (4)” bioavailability had the potential to be promotional. The review team did not believe that (b) (4) bioavailability was an inherent advantage and therefore changed the language to note that the bioavailability is “different.” The labeling still clearly conveys the corresponding doses.
- Based on a review of literature concerning the use of buprenorphine in pregnant and nursing women, the Maternal Health Team made recommendations to revise the relevant sections of labeling. These were also brought into the current format recommended by the MHT.

(b) (4)

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

- Regulatory Action  
Approval
- Risk Benefit Assessment

The Applicant has provided adequate evidence to support that Zubsolv will be safe and effective when used according to the agreed upon product labeling and within the limits of the agreed upon REMS. It will provide an additional treatment option for a patient population that suffers from a serious and life threatening disorder. The risks of abuse, misuse, diversion, overdose and death due to buprenorphine are real for these patients and their communities; but these risks should be reasonably well managed under the REMS. Indeed, these are the

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same risks that these patients experience due to their opioid addiction, and in the setting of no real risk management in that case. The benefits of allowing Zubsolv to be marketed to this patient population outweigh the risks. However, we will continue to monitor and assess the abuse and misuse of buprenorphine-containing products and, if the risk to benefit balance is no longer positive at some time point in the future, additional risk management tools will be considered, up to and including removal of these drugs from the market.

- Postmarketing Risk Management Activities

The following summary of the REMS for Zubsolv has been reproduced from pages 14 through 16 of Dr. Winchell's review:

Prior to market withdrawal, the reference product, Suboxone tablets, was marketed subject to a Risk Evaluation and Mitigation Strategy (REMS). Suboxone film continues to be marketed under the Suboxone/Subutex REMS, while approved generics of Suboxone and Subutex participate in a shared REMS program. 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 will be obliged to participate in the shared system, known as the BTOD (buprenorphine-containing transmucosal products for opioid dependence) REMS, but NDA holders are not subject to this requirement.

The Agency requested that Orexo join the shared system REMS to reduce the burden on the healthcare system by limiting the number of REMS for this class of products to two.

However, Orexo initially declined this request because they believed that their proposed REMS for Zubsolv was more robust than any of the approved programs. They provided a proposal based a failure mode and effects analysis (FMEA) conducted using the Suboxone REMS program to identify deficiencies and potential areas for enhancement. The Division of Risk Management (DRISK) and the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the Sponsor's FMEA submission to determine whether there was sufficient evidence to require the proposed changes. However, their evaluation identified that the FMEA was incomplete and lacked critical information to perform a full evaluation. In addition, DRISK determined that if an adequate FMEA analysis identified necessary improvements to the existing REMS, these improvements would be required for the class as whole (i.e., Suboxone/Subutex REMS and BTOD REMS).

Therefore, DRISK informed Orexo that their REMS would require the same elements as the BTOD REMS; and requested that the Orexo join the BTOD REMS to minimize burden on stakeholders. Orexo agreed to join the BTOD REMS. .

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Orexo has indicated to the Agency that they intend to join the BTOD REMS and begun the administrative process with the Buprenorphine Products Manufacturers Group (BPMG) to become an active member. However, the process will involve additional legal agreements among the BPMG and submission of a REMS modification to amend the BTOD materials to incorporate information about Zubsolv. Therefore, in the interim, Orexo submitted a proposed REMS that is identical in its elements to the BTOD REMS but incorporates appropriate Zubsolv-specific information into the REMS tools. The interim REMS has been reviewed by DRISK, and is acceptable. Orexo will be responsible for implementing the interim REMS until Orexo is an active member of the BPMG and submits a REMS modification that includes the BTOD REMS. Once Orexo joins the BPMG, Zubsolv will have its own product-specific Medication Guide; all other elements of the REMS will be shared.

The elements are shown below in text from Dr. Winchell's review.

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:

Medication Guide

- Postmarketing Study Requirements

A Thorough QT Study of buprenorphine's effect on cardiac conduction at doses used to treat addiction will be required as a Postmarketing Study Requirement.

- Postmarketing Commitments

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The Applicant has agreed to revise and validate the analytical method for organic impurities in the Naloxone API of the drug product accordingly to reflect an accuracy of (b) (4) RSD and intermediate precision of (b) (4) RSD.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BOB A RAPPAPORT  
07/03/2013