

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204242Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 12, 2013
From	Celia Winchell, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	204242
Applicant	Orexo AB
Date of Submission	September 5, 2012
PDUFA Goal Date	July 6, 2013
Proprietary Name / Established (USAN) names	Zubsolv buprenorphine and naloxone sublingual tablet
Dosage forms / Strength	5.7 mg buprenorphine/ 1.4 mg naloxone 1.4 mg buprenorphine/ 0.36 mg naloxone
Proposed Indication(s)	Maintenance treatment of opioid dependence
Recommended:	<i>Approval</i>

1. Introduction.....	2
2. Background.....	2
2.1 Role of Naloxone	3
2.2 Legal and Regulatory Issues Constraining Buprenorphine Treatment	4
2.3 Review Priority Designation.....	5
3. CMC.....	6
3.1 General product quality considerations	6
3.1.1. Drug Substances.....	6
3.1.2 Drug Product.....	7
3.1.3 Expiration Dating.....	8
3.1.4 Outstanding Product Quality Issues.....	8
3.2 Facilities review/inspection	8
4. Nonclinical Pharmacology/Toxicology	8
5. Clinical Pharmacology/Biopharmaceutics.....	9
5.1 General Background	9
5.2 Clinical Pharmacology Findings.....	9
5.3 QT assessment	10
6. Clinical Microbiology.....	10
7. Clinical/Statistical- Efficacy	11
8. Safety	12
9. Advisory Committee Meeting.....	13
10. Pediatrics.....	13
11. Other Relevant Regulatory Issues.....	14
11.1 Reference to Previous Agency Findings under §505(b)(2)	14
11.2 Risk Evaluation and Mitigation Strategy	14
11.3 Maternal Health Team Review	16
11.4 OSI inspection.....	16
11.5 Cardiac conduction effects.....	16
3. Labeling	16
4. Recommendations/Risk Benefit Assessment.....	18

1. Introduction

This application is for a new formulation of buprenorphine/naloxone combination sublingual tablets for the maintenance treatment of opioid dependence, referencing the approved product Suboxone (buprenorphine/naloxone) tablets (NDA 20733) through the 505(b)(2) pathway¹. The drug product was designated OX219 during development; the proprietary name, Zubsolv, has been found acceptable.

Like Suboxone, this is a sublingual tablet dosage form, but due to differences in bioavailability, the nominal doses are lower than those in Suboxone. Comparative pharmacokinetic studies have demonstrated exposure meeting criteria for bioequivalence, and the application rests on the Agency's previous findings of safety and efficacy of Suboxone.

Two dosage strengths are proposed for marketing. These are

- 5.7 mg buprenorphine/ 1.4 mg naloxone (corresponds to 8 mg/ 2 mg Suboxone tablet)
- 1.4 mg buprenorphine/ 0.36 mg naloxone (corresponds to 2 mg/ 0.5 mg Suboxone tablet)

ZUBSOLV sublingual tablets should be used in patients who have already begun treatment using buprenorphine-only sublingual products. The recommended dose is 11.4 mg/2.8 mg buprenorphine/naloxone/day (two 5.7/1.4 mg tablets) as a single daily dose, but may be adjusted for the individual patient. The usual dose range is 2.8 mg/0.72 mg buprenorphine/naloxone to 17.1 mg/4.2 mg buprenorphine/naloxone.

This review will briefly summarize the clinical pharmacology findings, safety findings from the pharmacokinetic studies in healthy, naltrexone-blocked volunteers, and a literature review supporting the adequacy of the naloxone dose.

2. Background

Buprenorphine is a partial agonist at the μ -opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain², two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence³, and a sublingual film formulation for opioid dependence⁴ and an extended-release transdermal film formulation for pain⁵ 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

¹ Suboxone tablets have been withdrawn by the manufacturer, Reckitt Benckiser, from US marketing. However, the Agency has determined that Suboxone tablets were not withdrawn from sale for reasons of safety or effectiveness and the product is listed in the "Withdrawn Applications" section of the Orange Book.

² Buprenex, NDA 18401 Reckitt Benckiser

³ Subutex (buprenorphine sublingual tablets), NDA 20732 and Suboxone (buprenorphine/naloxone sublingual tablets), NDA 20733, Reckitt Benckiser

⁴ Suboxone (buprenorphine naloxone) film, NDA 22410, Reckitt Benckiser

⁵ Butrans, NDA 21306

agonist at the μ -receptor. Like methadone, buprenorphine's activity at the μ -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.

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.

2.1 Role of Naloxone

As noted above, although buprenorphine has the potential to precipitate withdrawal symptoms in individuals dependent on full agonists, naloxone was included in the Suboxone formulation with the aim of providing an additional measure of deterrence to intravenous misuse. The naloxone is intended to be inactive when the product is used as intended, sublingually. Some sublingual absorption of naloxone is possible, however, and for this reason, it is recommended that patients transitioning from full opioids at the beginning of treatment be treated initially with a few days of a buprenorphine-only product (e.g. Subutex or generics). Because naloxone competes poorly with buprenorphine at the mu receptor, once a patient is maintained on buprenorphine, the combination product can be introduced.⁶ Naloxone is intended to produce aversive symptoms if the product is crushed and injected.

⁶ Studies supporting the reference product, Suboxone, either used a buprenorphine-only sublingual solution (no naloxone at all in the study), or, in one study, introduced Suboxone after two days of Subutex. Therefore, the labeling recommends this approach. It is becoming more common in clinical practice to perform direct induction (treatment initiation) with Suboxone, and several sponsors of buprenorphine/naloxone combination products, including Orexo, are pursuing studies to show that Suboxone is as well-tolerated in initial use as Subutex. However, at this time, combination products are labeled for use after initial treatment with buprenorphine-only products.

The current Agency approach to evaluating the abuse deterrent properties of drug products was not in place in 2002, when Suboxone tablets were approved. Because both buprenorphine and naloxone have the potential to precipitate withdrawal in opioid-dependent individuals, the contribution of naloxone to abuse-deterrence has not been definitively established. However, the referenced application provided evidence from laboratory studies that the amount of naloxone included in the formulation was capable of producing aversive effects when given in combination with buprenorphine. Ratios of 2:1, 4:1, and 8:1 (buprenorphine:naloxone) were evaluated and the 4:1 ratio was commercialized. However, it is likely that even if the ratio were to be maintained, there are doses of naloxone which are too low to cause significant aversive effects.

During the IND stage, Orexo was told that as long as the naloxone exposure was no higher than in the reference product, no safety or efficacy issues would arise. However, information would be needed showing that the amount of naloxone in the final formulation was sufficient to produce an aversive effect. At the pre-NDA meeting, Orexo was told that a literature-based approach to supporting the adequacy of the naloxone content would be acceptable.

2.2 Legal and Regulatory Issues Constraining Buprenorphine Treatment

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

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

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

IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

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

2.3 Review Priority Designation

Orexo initially indicated that they expected that this application might be accorded priority review because of the lower quantity of buprenorphine contained in each tablet compared to the reference product. It was their view that the lower dose might be safer or less likely to be diverted. However, it is known that individuals who misuse Suboxone or Subutex very commonly divide the tablets for use into halves or even quarters, which they may use sublingually, intranasally, or intravenously. Therefore, even the 1.4 mg or 5.7 mg quantities of buprenorphine in these tablets are more than adequate for individuals to abuse.

Another concern related to Suboxone and Subutex tablets is the recent increase in reports of accidental pediatric exposures. Again, Orexo hoped that the lower buprenorphine content would confer a safety advantage, but they were informed that the doses were still high enough to cause significant harm in the circumstance of accidental exposure.

At the time of submission, Orexo proposed that the application be designated as a priority review, not because of the buprenorphine content, but because of the packaging.

Zubsolv tablets are provided in blister packaging [REDACTED] (b) (4)

[REDACTED] The blister packaging is offered as a deterrent to accidental pediatric exposure. However, 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 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.

Therefore, although blister packaging has a number of favorable features, it was not sufficient to warrant a priority review designation for this application.

3. CMC

The CMC review was conducted by Julia C. Pinto, Ph.D., of the Office of New Drug Quality Assessment (ONDQA) Division III, supervised by Prasad Peri, Ph.D.

Dr. Pinto concluded that although sufficient CMC information to assure the identity, strength, purity, and quality of the drug product has been provided in this NDA submission, concerns remain regarding the analytical method for the naloxone assay in the drug product. Information requests have been sent the issue may be resolvable prior to the action date.

Additionally, although site inspections are complete, the Office of Compliance has not yet made an overall recommendation.

Therefore, the ONDQA team recommends approval, provided the deficiencies can be addressed and a satisfactory overall recommendation is received from the Office of Compliance.

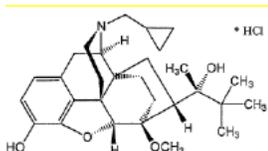
3.1 General product quality considerations

3.1.1. Drug Substances

The first drug substance is buprenorphine HCl, manufactured by (b) (4).

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

Molecular Weight: 467.6 (Base) 504.1 (salt)

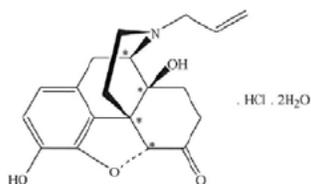


The drug substance is a white to almost white crystalline powder with only one polymorphic form. Reference to DMF (b) (4) is provided and the DMF has been reviewed and found adequate.

The second drug substance is naloxone HCl, manufactured by (b) (4).

Molecular formula: $C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$

Relative molecular weight: 399.9



The drug substances are (b) (4) and (b) (4).

3.1.2 Drug Product

Zubsolv sublingual tablets are rapidly disintegrating tablets with (b) (4) properties. There are two strengths, 1.4mg buprenorphine/0.36mg naloxone and 5.7mg buprenorphine/1.4mg 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.

Figure 1: Tablet Shape and Debossing



The manufacturing process consists of (b) (4) steps, which include (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.

Notably, the flavoring is described as (b) (4) in labeling and on the packaging, where a (b) (4) further conveys this impression. Dr. Pinto notes that (b) (4) and menthol are not the same, and recommends changing references from (b) (4) to “menthol.” This would seem to render the (b) (4) graphic inappropriate. If Orexo chooses not to identify the product as “menthol” on the carton, it would be acceptable to omit reference to the flavor.

3.1.3 Expiration Dating

The tablets are packaged in blister packages in sheets of 10 with 3 sheets to one carton. Orexo requested expiry of 18 months for the low strength, which was supported by real time data. They requested expiry of (b) (4) months for the higher strength, but did not provide data to support this. Therefore, ONDQA recommends an expiry of 18 months for both tablets.

(b) (4)

(b) (4)

3.1.4 Outstanding Product Quality Issues

Dr. Pinto identified issues with the analytical methods used to determine assay content for naloxone and related impurities in the drug product that require further revision and validation.

3.2 Facilities review/inspection

Zubsolv sublingual tablets are manufactured by Orexo AB and Orexo's US Contract Manufacturing Organization (CMO) AAIPharma Services Corp.

Orexo conducts manufacturing of bulk tablets, drug product release testing, final batch release and stability testing of the drug product in Uppsala, Sweden. Testing of raw materials and microbiological testing for Orexo is performed by (b) (4) and the blistering, packaging and labeling are performed by AAIPharma in Wilmington, NC. AAIPharma conducts testing of raw materials, manufacturing of bulk tablets, packaging and labeling, batch release and stability testing of the drug product.

The Office of Compliance has recommended all these sites as satisfactory, except for the Orexo site. The recommendation for the Orexo facility and the Overall recommendation are pending.

4. Nonclinical Pharmacology/Toxicology

- *No new non-clinical data were submitted.*

5. Clinical Pharmacology/Biopharmaceutics

5.1 General Background

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

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

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 ₀₋₄₈ , 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.

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_{max} , AUC_t, and AUC_{inf}) 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_{max} , 12% lower naloxone AUC_t, and 16% lower naloxone AUC_{inf} 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_{max} 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_t and AUC_{inf} over the range of 0.36 mg and 2.8 mg. C_{max} 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 QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points. This signal for QT prolongation was considered to meet the threshold for regulatory concern, but was not of clear clinical significance. The dose studied was significantly lower than the dose used for treating drug addiction; however, the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has not yet been evaluated in formal thorough QT studies. Such studies have been requested of 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.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

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

The adequacy of the naloxone dose to perform as intended—that is, to cause aversive effects if the product is crushed and injected—was supported by several published studies of naloxone-precipitated withdrawal, and by an extraction study showing that buprenorphine was not preferentially extracted from the drug product.

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)

[REDACTED]

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 0.33 mg naloxone and 1.14 mg BUP was released.”

The ability of naloxone doses of 0.33 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 μ -agonists (9 on methadone, 1 on morphine, 1 on hydromorphone, and 1 on tramadol) with parenteral doses of ≤ 0.33 mg naloxone
- Of these 12 studies, 10 showed evidence of precipitated withdrawal with ≤ 0.3 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 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 papillary 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. The labeling should be revised to indicate that a withdrawal syndrome is likely, but to remove phrases such as “(b) (4)” and “(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.

8. Safety

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.

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 ^a 11.4/2.8 ^b			OX219 All	Suboxone [®]	
OX219-001	18	-	-	-	-	-	-	18	18
OX219-002	-	23	24	-	-	-	-	47	22
OX219-003	-	-	-	-	53	-	-	53	60
OX219-004 ^c	-	-	-	45	46	45	44	180	-
Total	18	23	24	45	99	45	44	298	100

^a 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

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

^c 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.

9. Advisory Committee Meeting

N/A

10. Pediatrics

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. The Sponsor submitted an analysis of medical claims databases and found a prevalence of 0.25 per 1000 in private data and 0.05 per 1000 in Medicaid data for age 1-11.

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.

Table 2: Population estimate of the numbers of individuals in the US projected to meet criteria for prescription opioid dependence, by age, from 12-16 (NSDUH)

(Data were provided courtesy of Scott Novak, PhD, from RTI, which manages NSDUH for the Substance Abuse and Mental Health Services Administration.)

<u>Age</u>	<u>Population Estimate (rounded to nearest hundred)</u>
12	4,800
13	7,700
14	10,600
15	20,000
16	39,000

Orexo also commissioned an estimate of prevalence from Medicaid claims data and received an estimate of 0.506 per 1000 beneficiaries.

Orexo also evaluated the likelihood of enrollment success, citing a prior study in literature, concluding that it would take ten years to complete the necessary enrollment in six sites.

The Division concurred that based on the most recent prevalence estimates and current and previous feasibility assessments, studies would be highly impracticable. This information was provided to the Pediatric Review Committee (PeRC), who agreed that a waiver should be granted.

11. Other Relevant Regulatory Issues

11.1 Reference to Previous Agency Findings under §505(b)(2)

Orexo has referenced the Suboxone (NDA 20733) in this application, intending for the application to rest in part on the agency's previous findings of safety and efficacy for sublingual buprenorphine/naloxone tablets. Suboxone tablets have been withdrawn by the manufacturer, Reckitt Benckiser, from US marketing. However, the Agency has determined that Suboxone tablets were not withdrawn from sale for reasons of safety or effectiveness⁷. The referenced application is now listed in the Discontinued section of the Orange Book.

11.2 Risk Evaluation and Mitigation Strategy

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

⁷ 78 Fed. Reg. 34108 (June 6, 2013).

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. .

The REMS proposal was reviewed by Jason Bunting, PharmD., whose review will discuss in greater detail the differences between the Applicant's proposal and the existing REMS. DRISK has not yet received a submission supporting adding Zubsolv to the BTOD REMS and therefore has not yet completed their review at this time.

The goals of the REMS are to:

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

REMS Elements:

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

Materials for Prescribers:

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

Materials for Pharmacists:

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

Materials for Patients:

1. Medication Guide

11.3 Maternal Health Team 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:

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.

11.4 OSI inspection

OSI inspected the clinical and analytical sites of study OX219-003 and concluded that the data are acceptable

11.5 Cardiac conduction effects

Orexo was informed during the IND stage that a signal for QT prolongation meeting criteria for regulatory significance had been identified in a study of another buprenorphine product, at a dose significantly lower than the dose used for treating drug addiction. A study of the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has been requested of Reckitt Benckiser as post-marketing requirement (PMR), but has not yet been completed. Orexo was informed that a TQT study would be required for their NDA if the information was not available to be incorporated by reference at the time of submission, but that the study could be performed post-approval.

3. Labeling

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:

- The Applicant proposed to include language instructing physicians to consider  (b) (4). Therefore, this recommendation was deleted.
- The Dosage and Administration section included language giving specific restrictions on the amount of drug that should be prescribed for take-home use, including statements such as  (b) (4).
- 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)  (b) (4)” because the studies submitted suggested that the reaction is likely in most, but not all, individuals, and that it may not be particularly intense.
- 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)

4. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action From a clinical standpoint, the application may be approved.
 - However, issues that require resolution at the time of this writing include
 - Arrangements for Orexo to join the BTOD REMS, and submission of REMS materials incorporating Zubsolv-specific information
 - Satisfactory response to CMC information requests concerning assay validation
 - Office of Compliance recommendation regarding manufacturing sites.

- Risk Benefit Assessment

This product provides the same systemic exposure to buprenorphine as the reference product, Suboxone tablets, and contains an amount of naloxone sufficient to produce aversive responses under conditions of intravenous misuse by many individuals with physical dependence on full opioid agonists. Its efficacy and benefit is expected to be the same as the reference product. It does not represent a new dosage form or route of administration, and does not present new safety concerns compared to the reference product. It similarly does not provide any major safety benefits to patients, and will likely be subject to diversion, misuse, and abuse similar to the reference product. The child-resistant blister packaging could potentially prove advantageous in preventing accidental exposure. A REMS misuse, abuse, and accidental overdose will be needed to ensure the benefits outweigh the risks.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

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

- Recommendation for other Postmarketing Requirements and Commitments

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

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

/s/

CELIA J WINCHELL
06/12/2013