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CLINICAL REVIEW

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Established Name buprenorphine and naloxone
(Proposed) Trade Name Zubsolv
Therapeutic Class opioid agonist and antagonist
Applicant Orexo AB

Formulation(s) sublingual tablet
Dosing Regimen once a day
Indication(s) maintenance treatment of
opioid dependence
Intended Population(s) patients with opioid
dependence

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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	6
1.1	Recommendation on Regulatory Action	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	6
1.4	Recommendations for Postmarket Requirements and Commitments	7
2	INTRODUCTION AND REGULATORY BACKGROUND	7
2.1	Product Information	8
2.2	Tables of Currently Available Treatments for Proposed Indications	9
2.3	Availability of Proposed Active Ingredient in the United States	9
2.4	Important Safety Issues With Consideration to Related Drugs.....	9
2.5	Summary of Presubmission Regulatory Activity Related to Submission	9
3	ETHICS AND GOOD CLINICAL PRACTICES.....	11
3.1	Submission Quality and Integrity	11
3.2	Compliance with Good Clinical Practices	11
3.3	Financial Disclosures.....	11
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	11
4.1	Chemistry Manufacturing and Controls	11
4.4	Clinical Pharmacology	12
5	SOURCES OF CLINICAL DATA.....	12
5.1	Tables of Studies/Clinical Trials	12
5.2	Review Strategy	12
6	REVIEW OF EFFICACY	14
	Efficacy Summary.....	14
7	REVIEW OF SAFETY.....	14
	Safety Summary	14
7.1	Methods.....	14
7.1.1	7.1.1 Studies/Clinical Trials Used to Evaluate Safety	14
7.1.2	7.1.2 Categorization of Adverse Events	15
7.1.3	7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	15
7.2	Adequacy of Safety Assessments	15
7.2.1	7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	15
7.2.4	7.2.4 Routine Clinical Testing	16
7.3	Major Safety Results	16

7.3.1	Deaths.....	16
7.3.2	Nonfatal Serious Adverse Events	16
7.3.3	Dropouts and/or Discontinuations	16
7.3.5	Submission Specific Primary Safety Concerns	17
7.4	Supportive Safety Results	18
7.4.1	Common Adverse Events	18
7.4.2	Laboratory Findings	19
7.4.3	Vital Signs	19
7.4.4	Electrocardiograms (ECGs)	20
7.6	Additional Safety Evaluations	20
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	20
9	APPENDICES	21
9.1	Literature Review/References	21
9.2	Labeling Recommendations	24

Table of Tables

Table 1 Studies Used to Evaluate Safety	14
Table 2 Exposure by Formulation and Dose	16
Table 3 Discontinuations due to Adverse Events	17
Table 4 Adverse Events in Studies 003 and 004.....	19
Table 5 Studies That Used 0.3 mg Naloxone or Less	22

Table of Figures

No table of figures entries found.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the review of clinical data and consideration of clinical issues, I recommend approval of the application.

The Combination Rule states that each component of a combination of two or more drugs must make a contribution to the claimed effects of the drug. The claimed effect of naloxone in the referenced application is to produce an aversive reaction under conditions of misuse. The lowest strength of Zubsolv contains less naloxone than the lowest strength of the referenced product. Therefore, the Applicant needed to provide evidence that the amount of naloxone that could be extracted from the lowest proposed strength would be sufficient to produce an aversive reaction under conditions of misuse.

The Applicant submitted adequate evidence based on literature review and an in vitro dissolution study to conclude that the naloxone contained in all proposed Zubsolv strengths is high enough to be expected to produce an aversive reaction under conditions of misuse in individuals dependent on full agonist opioids. Therefore, there is adequate support in the application to justify the combination of buprenorphine and naloxone at all proposed strengths.

The safety data collected in the clinical pharmacology studies reveals no safety concern with this new formulation of buprenorphine and naloxone.

1.2 Risk Benefit Assessment

The Applicant is relying on a previous Agency finding that the risk/benefit profile for Suboxone tablets is favorable. The clinical safety data from the clinical pharmacology studies do not alter the risk/benefit profile. The risk/benefit profile for including naloxone in the product at the proposed strengths remains favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is in place for the referenced product consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of REMS assessments. The goal of the REMS is to mitigate the risks of accidental exposure, misuse, and abuse. The elements to assure safe use are designed to inform patients of the serious risks associated with

buprenorphine/naloxone tablets and appropriate conditions of safe use and storage, and to ensure adequate clinical monitoring of patients by healthcare providers.

The review of the Applicant's proposed Risk Evaluation and Evaluation and Mitigation Strategy documents is in progress. See the Division of Risk Management review.

1.4 Recommendations for Postmarket Requirements and Commitments

The Agency is aware of data indicating that buprenorphine may cause QT interval prolongation at therapeutic concentrations. I recommend requiring that the Applicant conduct a thorough QT study to further evaluate this safety concern as a Postmarketing Requirement.

2 Introduction and Regulatory Background

Buprenorphine is a partial agonist at the μ -opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence, and a sublingual film formulation for opioid dependence and an extended-release transdermal film formulation for pain were approved in 2010.

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.

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ -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.

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 current Agency approach to evaluating the abuse deterrent properties of drug products was not in place in 2002, when Suboxone tablets were approved, and the evidence supporting the abuse-deterrent properties of Suboxone would not necessarily meet current standards for the approval of an abuse-deterrent drug product.

The recommended target dose for Suboxone tablets is 16/4 mg in a single daily dose. The maintenance dose can range from 4/1 mg to 24/6 mg per day and should be tailored to the individual patient. The recommended dose for treatment of pain is much lower, and for this reason, warnings against prescribing Suboxone for pain are part of the prescribing information.

2.1 Product Information

This product references the Agency's previous finding of efficacy and safety for Suboxone. The Applicant pursued the NDA pathway for approval rather than the ANDA pathway because the formulation is more bioavailable and contains less active ingredient than the reference product.

Two dosage strengths are proposed for marketing. These are

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

The Applicant has submitted clinical pharmacokinetic data intended to demonstrate that the 8 mg/ 2 mg strength of Suboxone is bioequivalent to the 5.7 mg/1.4 mg strength. A biowaiver has been requested to obviate the need for demonstration of bioequivalence between the lower strength of the Applicant's product and the lower strength of Suboxone tablets.

2.2 Tables of Currently Available Treatments for Proposed Indications

CURRENTLY AVAILABLE TREATMENTS FOR OPIOID DEPENDENCE			
Generic/Chemical Name	Trade Name	Sponsor	Dosage form(s)
Buprenorphine/naloxone	Suboxone (also generics)	Reckitt Benckiser	<ul style="list-style-type: none"> • Sublingual tablet • Sublingual film
Buprenorphine	Subutex (also generics)	Reckitt Benckiser	<ul style="list-style-type: none"> • Sublingual tablet
Methadone HCl	Methadose (also generic)	Mallinckrodt	<ul style="list-style-type: none"> • Oral solution • Bulk powder • Tablet • Dispersible tab
Methadone HCl	Dolophine (also generic)	Roxane	<ul style="list-style-type: none"> • Tablet • Oral concentrate • Oral solution
Naltrexone HCl	ReVia (also generics)	Duramed	<ul style="list-style-type: none"> • Tablet
Naltrexone HCl	Vivitrol	Alkermes	<ul style="list-style-type: none"> • Injectable suspension

2.3 Availability of Proposed Active Ingredient in the United States

Buprenorphine combined with naloxone is available as Suboxone tablets and Suboxone film. There are also generic versions of the tablets available.

2.4 Important Safety Issues With Consideration to Related Drugs

Oral transmucosal buprenorphine-containing products indicated for opioid dependence currently have a REMS. The REMS goals address the most important safety issues associated with these products and are:

- to minimize the risk of
 - accidental overdose, including pediatric exposure
 - misuse and abuse
- inform patients of the serious risks associated with the products, which also include:
 - respiratory depression, especially in combination with CNS depressants
 - liver function abnormalities

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Division provided the following advice during the development program

- Pre-IND meeting, February 3, 2011

- The most appropriate reference product is Suboxone tablets (NDA 20733)
- The firm may use the Suboxone film label as a guide for labeling (since at the time it was the most recently approved label)
- Buprenorphine exposure must be bioequivalent to obviate the need for clinical efficacy or safety data
- Naloxone exposure can be lower than the reference product without triggering the need for additional clinical safety data, but if it is higher, additional safety data will be required assessing whether it is causing aversive effects

(b) (4)

- Provide data demonstrating that your product releases sufficient naloxone under conditions of misuse to precipitate withdrawal in persons dependent on full agonist opioids
- You will not receive orphan designation and will be required to submit a pediatric plan under PREA
- Type C Response in Writing: October 4, 2011
 - Questions and responses covered CMC and Non-clinical issues
- Pre-NDA meeting, July 17, 2012
 - It is acceptable for norbuprenorphine exposure to be lower than the reference product
 - The exposure and assessments for local tolerability appear sufficient
 - Stating that patients should be initially inducted using buprenorphine sublingual tablets in the PI is acceptable
 - You will be required to conduct a tQT study as a PMR
 - You may submit a waiver request for pediatric studies with the following rationales or supporting information:
 - birth to 5 weeks: naloxone has no therapeutic value in neonates for the treatment of neonatal abstinence syndrome
 - 5 weeks to 12 years: lack of opioid dependence diagnosis in this population
 - 12 years to 16 years: pediatric use data of currently marketed buprenorphine/naloxone products demonstrating that it is not widely used and data showing the prevalence of opioid dependence in this age group is too low to make a study feasible
 - Suboxone tablets label has been updated and should be used as a guide instead of the film label

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no issues with the quality of the submission that affected my ability to complete my review.

3.2 Compliance with Good Clinical Practices

The Applicant reported that the four clinical pharmacology studies submitted in support of their NDA application were conducted in accordance with Good Clinical Practices

3.3 Financial Disclosures

The Applicant included financial disclosure information for all four clinical pharmacology studies. There were no reported financial interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In vitro dissolution study

Dr. Sun reviewed the results of Report 10 3299, an in vitro extraction study. The results showed that under all conditions, at 1, 5, and 10 minute time points, the 4:1 buprenorphine to naloxone ratio was not exceeded. Dr. Sun concluded that buprenorphine does not appear to be preferentially extracted. See Dr. Sun's review for further details.

Disintegration test

In the Biopharmaceutics review, Dr. Khairuzzaman concludes that based on the comparative data the Applicant provided, disintegration is an acceptable alternative quality test to dissolution.

Biowaiver request

Dr. Khairuzzaman also concluded that the formulation composition information and dissolution profile data adequately support the biowaiver request and recommends approval of the biowaiver for the 1.4 mg/ 0.36 mg strength.4.3 Preclinical Pharmacology/Toxicology

The proposed drug product did not trigger the need for new preclinical pharmacology or toxicology data.

4.4 Clinical Pharmacology

The Applicant has submitted clinical pharmacokinetic data intended to demonstrate that the 8 mg/ 2 mg strength of Suboxone is bioequivalent to the 5.7 mg/ (b) (4) mg strength. The Clinical Pharmacology review team has made a preliminary finding that the Applicant has demonstrated bioequivalence for buprenorphine.

The preliminary Clinical Pharmacology bioequivalence conclusions are as follows:

1. Zubsolv 5.7/1.4 mg sublingual tablet exhibited equivalent systemic exposure to buprenorphine in comparison to the referenced product, 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.

Lower naloxone exposure is acceptable because naloxone is intended to be inactive when the product is used as intended. For further information about the function of naloxone see section 2.1 Product Information. Because the naloxone exposure was not higher than the referenced product, no additional clinical safety data is required. See the Clinical Pharmacology review for full results and conclusions.

The Applicant has requested a biowaiver for the proposed lower strength of 1.4 mg/ 0.36 mg. See section 4.1 Chemistry Manufacturing and Controls for the biopharmaceutics review conclusions and recommendations.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were no studies included in the application to inform clinical efficacy. The table of clinical pharmacology studies used to evaluate safety is located in Studies/Clinical Trials Used to Evaluate Safety

5.2 Review Strategy

There are two clinical issues addressed in this review.

The first issue is the role of naloxone in Zubsolv. Naloxone is a potent opioid antagonist with high affinity for the mu opioid receptor. Injected buprenorphine and naloxone in a 4:1 ratio has been shown to cause opioid withdrawal symptoms in subjects dependent on the full mu opioid agonists, methadone and morphine. In the sublingual tablet formulations, the naloxone is intended to be inactive when the product is used

sublingually as intended due to poor sublingual absorption. It is meant 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 than would occur if the product only contained buprenorphine. This added abuse deterrence would not be expected to extend to all opioid-dependent persons. Those with a low level of full mu opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine would be expected to be able to abuse buprenorphine/naloxone combinations by the intravenous or intranasal route without the strong aversive experience noted in the studies. Epidemiologic and anecdotal evidence indeed indicates that some opioid users insufflate or inject buprenorphine/naloxone combination products without experiencing aversive reactions that deter further misuse.

Zubsolv, like Suboxone tablets, contains buprenorphine and naloxone in the 4:1 ratio that was shown to be capable of causing opioid withdrawal symptoms in those with sufficiently high full mu agonist dependence. Therefore, the ratio the Applicant chose is not of concern.

However, the amount of naloxone in Zubsolv is less than the naloxone in the corresponding strength of Suboxone sublingual tablets. The lowest dose of Suboxone contains 0.5 mg of naloxone and the lowest dose of Zubsolv contains 0.36 mg naloxone.

Each active ingredient in a combination product must provide a therapeutic benefit. In the case of Suboxone, the review team found that naloxone had a benefit for the approved indication of maintenance treatment of opioid dependence, because it could decrease the likelihood that people dependent on full opioid agonists would use it by the intravenous route, which would be a misuse of the product. The Applicant cannot rely on the previous Agency finding that naloxone will contribute to discouraging misuse, because the dose available for extraction and injection from the Applicant's product is lower than from the reference product and may not be large enough to cause an aversive reaction even in those dependent on full agonists. Therefore, the Applicant needed to show that this smaller injected dose of naloxone would be expected to produce an aversive reaction when injected.

To determine whether the dose of naloxone in Zubsolv is acceptable, I reviewed the report titled "Qualitative Systematic Review of the Minimum Effective Dose of Naloxone to Precipitate Withdrawal in Persons Physically Dependent on Opioids" in 9.1 Literature Review/References.

The second issue is the safety of the drug product. The Applicant is relying on the previous finding of safety for the safety of the drug substance and route of administration. Because the exposure to buprenorphine and naloxone from the new formulation fall into the range demonstrated to be safe under the referenced IND, this is appropriate and extensive evaluation of systemic safety was not required. All studies

were conducted in volunteers who received naltrexone to block the systemic effects of buprenorphine, and therefore the systemic adverse events are unlikely to be revealing. This review will evaluate any evidence of local adverse reactions to this new sublingual formulation by reviewing the safety data from the clinical pharmacology studies. This issue is discussed in section 7 of the document.

Deleted sections

I deleted sections 2.6, 4.2, 4.3, 4.4.1, 4.4.2, 4.4.3, 5.3, 6.1, 7.2.2, 7.2.3, 7.2.5, 7.2.6, 7.3.4, 7.4.5, 7.4.6, 7/5, 7.6.1, 7.6.2, 7.6.3, 7.7, and 9.3 because they were not relevant to this application.

6 Review of Efficacy

Efficacy Summary

The Applicant is relying on the previous finding of efficacy for Suboxone (NDA 20733) and has provided a bridge between Suboxone and Zubsolv based on clinical pharmacology data.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 1 Studies Used to Evaluate Safety

Study Identifier	Study Purpose	Study Population	Formulation	Safety Assessments
OX219-001	comparative PK OX219 and Suboxone tab	N=18 healthy males, naltrexone blocked	OX219-1	Adverse events, SAEs, Local

Study Identifier	Study Purpose	Study Population	Formulation	Safety Assessments
OX219-002	comparative PK OX219 and Suboxone tab	N=24 healthy males and females, naltrexone blocked	OX219-3	tolerability, Clinical chemistry, Hematology, Vital signs, ECG, Physical exams, Premature withdrawal
OX219-003	comparative absorption OX219 and Suboxone tab	N = 60 healthy subjects, naltrexone blocked	OX219-4	
OX219-004	dose proportionality	N=61 healthy males and females, naltrexone blocked	OX219-4	

7.1.2 7.1.2 Categorization of Adverse Events

Adverse events are classified using MedDRA version 15.0

7.1.3 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data was pooled in two ways:

- All four studies
- Studies 003 and 004 (used final commercial product)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the final commercial product, there were 233 single dose exposures in 114 subjects. There were 53 exposures in 53 subjects in Study 003 and 180 exposures in 61 subjects in Study 004. This is adequate to assess the local effects of the product. The table below summarizes all exposures in the development program.

Table 2 Exposure by Formulation and Dose

Study	Formulation / Dose [mg buprenorphine / mg naloxone]							OX219 All	Suboxone [®]
	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					
OX219-001	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

7.2.4 Routine Clinical Testing

The Applicant assessed local tolerability by visual inspection of the sublingual area prior to and at 1, 8, and 24 hours after dosing with the study drug. Findings were recorded as normal or abnormal. Investigators in study 004 were trained to perform assessments by a dental professional and a dentist performed local tolerability assessments in study 003.

7.3 Major Safety Results

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

7.3.1 Deaths

None

7.3.2 Nonfatal Serious Adverse Events

None

7.3.3 Dropouts and/or Discontinuations

The development program mainly consisted of single exposures in naltrexone-blocked subjects and there were no studies with multiple consecutive dosing. 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 dropouts or discontinuations reported in Study 004 due to an adverse event of the oral cavity.

There were 14 discontinuations due to 19 adverse events. The adverse events that led to discontinuations are summarized below by study and last treatment received preceding the event. There were no discontinuations due to adverse events in Study OX219-001. In Study OX219-002, one subject discontinued for emesis, vasovagal reaction and myalgia. In Study OX219-003, one subject had weakness, nausea, and dizziness. In Study OX219-004, one subject had nausea and vomiting. All other subjects who discontinued for adverse events had only one event as the reason for discontinuation. In the table below, all 19 adverse events that led to discontinuation are counted.

Table 3 Discontinuations due to Adverse Events

	Study	OX219-002		OX219-003		OX219-004
	Study Drug	OX219	Suboxone	OX219	Suboxone	OX219
	Number of discontinued subjects	1	0	0	3	8
Adverse Event	Emesis	1			1	4
	Nausea				1	2
	Vasovagal reaction	1				1
	Headache					1
	Myalgia	1				
	Weakness				1	
	Dizziness				1	
	Toothache				1	
	Anemia					1

Source: ISS p. 41-42

Subjects received naltrexone blockade in all studies. Adverse events like nausea, emesis, dizziness, and headache are known to be associated with opioids, but may also be associated with naltrexone. Vasovagal reaction can be associated with blood sample collection. There were no unusual trends in discontinuations due to adverse events that would suggest a unique safety issue with OX219.

7.3.5 Submission Specific Primary Safety Concerns

Local tolerability

Five subjects had an abnormal exam finding in the development program. All abnormal findings were present at baseline and were identified in Study 003, which is the only

study where a dentist performed the assessments. No local tolerability concerns emerged from the available data.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant identified no new safety signals from the safety data collected in the clinical pharmacology studies. The proposed section 6 labeling is identical to Suboxone tablets.

Opioid-related adverse events would be expected to be minimized in all studies because all subjects received naltrexone, an opioid antagonist, to block the opioid-related effects of buprenorphine. Therefore, these results are not useful in anticipating what mu-opioid receptor-mediated adverse events could be expected in people taking this product without naltrexone blockade.

Below are the adverse events that occurred in more than one subject by treatment group for the studies using the final commercial product. The adverse events were similar between groups.

Table 4 Adverse Events in Studies 003 and 004

System Organ Class Preferred Term	OX219-4 1.4/0.36 (N= 45)	OX219-4 5.7/1.4 (N= 99)	OX219-4 8.5/2.12 (N= 45)	OX219-4 11.4/2.8 (N= 44)	All OX219-4 (N=233)	Suboxone® (N= 60)
Gastrointestinal Disorders	16 (35.6%)	30 (30.3%)	19 (42.2%)	19 (43.2%)	84 (36.1%)	26 (43.3%)
Abdominal Pain	6 (13.3%)	3 (3.0%)	5 (11.1%)	4 (9.1%)	18 (7.7%)	2 (3.3%)
Abdominal Pain Upper	0 (0.0%)	3 (3.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)	1 (1.7%)
Diarhea	2 (4.4%)	1 (1.0%)	2 (4.4%)	3 (6.8%)	8 (3.4%)	0 (0.0%)
Dry Mouth	1 (2.2%)	1 (1.0%)	3 (6.7%)	0 (0.0%)	5 (2.1%)	5 (8.3%)
Nausea	11 (24.4%)	24 (24.2%)	11 (24.4%)	18 (40.9%)	64 (27.5%)	20 (33.3%)
Vomiting	2 (4.4%)	10 (10.1%)	3 (6.7%)	5 (11.4%)	20 (8.6%)	8 (13.3%)
General Disorders And Administration Site Conditions	3 (6.7%)	4 (4.0%)	2 (4.4%)	8 (18.2%)	17 (7.3%)	4 (6.7%)
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.0%)
Fatigue	1 (2.2%)	1 (1.0%)	1 (2.2%)	3 (6.8%)	6 (2.6%)	2 (3.3%)
Infusion Site Extravasation	0 (0.0%)	0 (0.0%)	1 (2.2%)	3 (6.8%)	4 (1.7%)	0 (0.0%)
Metabolism And Nutrition Disorders	3 (6.7%)	5 (5.1%)	5 (11.1%)	3 (6.8%)	16 (6.9%)	0 (0.0%)
Decreased Appetite	3 (6.7%)	5 (5.1%)	5 (11.1%)	3 (6.8%)	16 (6.9%)	0 (0.0%)
Nervous System Disorders	10 (22.2%)	24 (24.2%)	11 (24.4%)	16 (36.4%)	61 (26.2%)	28 (46.7%)
Dizziness	4 (8.9%)	13 (13.1%)	7 (15.6%)	8 (18.2%)	32 (13.7%)	19 (31.7%)
Headache	7 (15.6%)	11 (11.1%)	5 (11.1%)	7 (15.9%)	30 (12.9%)	10 (16.7%)
Paresthesia	1 (2.2%)	0 (0.0%)	0 (0.0%)	2 (4.5%)	3 (1.3%)	1 (1.7%)
Somnolence	2 (4.4%)	5 (5.1%)	1 (2.2%)	1 (2.3%)	9 (3.9%)	5 (8.3%)
Psychiatric Disorders	1 (2.2%)	5 (5.1%)	0 (0.0%)	3 (6.8%)	9 (3.9%)	3 (5.0%)
Euphoric Mood	0 (0.0%)	3 (3.0%)	0 (0.0%)	0 (0.0%)	3 (1.3%)	2 (3.3%)
Respiratory, Thoracic And Mediastinal Disorders	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (4.5%)	4 (1.7%)	0 (0.0%)
Oropharyngeal Pain	0 (0.0%)	2 (2.0%)	0 (0.0%)	1 (2.3%)	3 (1.3%)	0 (0.0%)
Vascular Disorders	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (4.5%)	4 (1.7%)	1 (1.7%)
Flushing	0 (0.0%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)	1 (1.7%)

Source: Table 11, ISS

7.4.2 Laboratory Findings

No safety signals emerged from the limited laboratory data collected in the clinical pharmacology studies.

7.4.3 Vital Signs

No safety signals emerged from the vital sign data collected in the clinical pharmacology studies.

7.4.4 Electrocardiograms (ECGs)

The clinical development program was not designed to evaluate the risk of QT prolongation. See section 1.4 Recommendations for Postmarket Requirements and Commitments for recommendations regarding a Postmarketing Requirement for a thorough QT study.

7.6 Additional Safety Evaluations

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Dr. Sun evaluated the abuse-related information in the application and concluded that additional evaluation of the product's abuse potential is not warranted and the Applicant may rely on the Agency's previous findings regarding the abuse-related risk profile for the referenced drug.

Dr. Sun noted that the Applicant is not proposing abuse-deterrent claims in product labeling. He outlined what further evaluation would be required if the Applicant wished to seek additional labeling claims in the future.

For details, see Dr. Sun's review.

9 Appendices

9.1 Literature Review/References

Qualitative Systematic Review of the Minimum Effective Dose of Naloxone to Precipitate Withdrawal in Persons Physically Dependent on Opioids

The Applicant conducted an in vitro dissolution study¹ to demonstrate that nearly all the naloxone is extracted from the Zubsolv tablet. None of the extraction methods preferentially extracted buprenorphine over naloxone. These results indicate that attempts to inject Zubsolv will result in exposure to naloxone. The Applicant estimates that (b) (4) will be available for injection out of the lowest strength, which contains 0.36 mg naloxone. Some methods extracted (b) (4) of naloxone. These methods also extracted less buprenorphine and therefore would be expected to be less attractive. Other methods extracted all 0.36 mg of naloxone and it is reasonably conservative to use the (b) (4) naloxone figure when exploring the available literature.

The Applicant reviewed the literature support for a dose of (b) (4) causing withdrawal symptoms in opioid dependent subjects.

Methods: PubMed search using appropriate search terms

Literature Search Results:

- 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.

¹ Report 10 3299 naloxone extraction in small volumes from Ox219 low strength sublingual tablets, Module 3, Section 3.2.P.2.2

Table 5 Studies That Used (b) (4) Naloxone or Less

Reference	Opioid	Naloxone Dose and Route
Evidence of Aversive Effects		
Greenwald 2005	Methadone	0.1 mg IV
Kanof 1992		0.05, 0.1, 0.15, 0.2 mg IV
Mendelson 1997		0.1 mg IV
Preston 1988		0.1 mg, 0.2 mg IM
Preston 1988		0.2 mg SC
Preston 1989		0.1 mg, 0.2 mg IM
Rosado 2007		0.2 mg IM
Schuster 1995		0.2 mg IM
Strain 1992		0.1 mg, 0.2 mg IM
Schuh 1996	Morphine	0.3 mg
No Evidence of Aversive Effects		
Stoller 2001	Hydromorphone	0.25 mg
Lanier 2010	Tramadol	0.25, 0.5, 1 mg

Source: Adapted from 5.3.5.4 Qualitative Systematic Review of the Minimum Effective Dose of Naloxone to Precipitate Withdrawal in Persons Physically Dependent on Opioids Table 1

Studies supportive of the adequacy of parenteral naloxone (b) (4) to produce aversive effects in individuals dependent on full agonists

The most information on the aversive effects of parenteral doses of naloxone (b) (4) and less is available in subjects dependent on methadone. Nine out of ten of the studies that showed evidence of precipitated withdrawal studied methadone.

The Applicant needs to provide evidence that can be expected to be generalizable to situations that would arise with misuse of Zubsolv in the general population. Because of methadone's unique characteristics, it is not the ideal opioid to demonstrate this type of generalizability.

Therefore, the study in morphine-dependent subjects is of particular interest. Morphine is the prototypical short-acting full mu agonist. In the Schuh publication, subjects were opioid-dependent volunteers and 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.

Studies not supportive of the adequacy of parenteral naloxone (b) (4) to produce aversive effects in individuals dependent on full agonists

- Stoller 2001: Subjects were maintained on 40 mg PO hydromorphone per day and did not experience precipitated withdrawal from 0.25 mg IM naloxone. The author comments that these results may be due to a low level of physical dependence on hydromorphone 40 mg per day.
- Lanier 2010: For subjects on tramadol, 0.25 mg naloxone did not produce withdrawal symptoms, but 0.5 mg and 1 mg naloxone did. Because tramadol is such a weak agonist, these results are less generalizable to all full mu agonists than the results from the Schuh publication.

While doses of (b) (4) mg naloxone did not produce withdrawal symptoms in all studies, the evidence presented supports the expectation that (b) (4) mg of injected naloxone would cause opioid withdrawal symptoms in some people dependent on μ -agonists, especially those dependent on methadone.

The study conducted in subjects dependent on morphine indicates that the effects of naloxone in doses of (b) (4) 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. Hydromorphone 40 mg PO per day would be similar to morphine 60 mg IM per day. Therefore, the highest doses tested in the Schuh study were roughly double the opioid dose in the Stoller study, which could partially account for the discordant results. Similarly, the highest doses in the Schuh study were roughly four to five times the opioid dose used in the Lanier study. It is reasonable to expect that in a real-world misuse situation, opioid-dependent people could be using sufficient opioids to have a level of physical dependence comparable to 120 mg IM morphine per day.

For naloxone to serve a purpose in Zubsolv, the amount of naloxone in the lowest proposed strength need not produce aversive effects for every possible level of physical dependence, no matter how low, or with every opioid, no matter how weak its affinity to the mu opioid receptor.

The submitted evidence is adequate to satisfy the requirement that naloxone serves a purpose in all proposed strengths of Zubsolv.

9.2 Labeling Recommendations

The label is based on the Suboxone tablet label and contains few changes. Substantive changes are discussed below.

Dosing and Administration: I recommend removing the statement [REDACTED] (b) (4)

[REDACTED] The Applicant did not provide support for including this recommendation in labeling but believes that [REDACTED] (b) (4)

Warnings and Precautions: Cases of fatal respiratory depression have occurred since the Suboxone tablet label was written. Therefore, the term “[REDACTED]” (b) (4) has been changed to “fatal” in 5.4 Unintentional Pediatric Exposure

Pregnancy and Nursing Mothers: See the Pediatric and Maternal Health Staff review for a discussion of the Pregnancy and Nursing Mothers section.

Pediatric Use: Language stating “This product is not appropriate for the treatment of neonatal abstinence syndrome in neonates, because it contains naloxone, an opioid antagonist” was added in accordance with PERC recommendations for labeling of products that receive a PREA waiver for safety reasons in a pediatric population.

Clinical Studies: To be consistent with the approach taken for other buprenorphine/naloxone products that relied on the previous findings of efficacy and safety of Suboxone tablets, I recommend omitting [REDACTED] (b) (4)

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

/s/

PAMELA J HORN
05/23/2013

CELIA J WINCHELL
05/24/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			X	eval of arrhythmogenic potential will be a PMR
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		not necessary due to small number AEs
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested)	X			no deaths or SAEs occurred, adverse

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				dropout narratives submitted
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			min effective dose naloxone review
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			waiver request for all age groups
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The following requests and comment should be conveyed to the Sponsor:

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

PAMELA J HORN
11/06/2012

CELIA J WINCHELL
11/06/2012