

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204242Orig1s000**

**OTHER REVIEW(S)**

505(b)(2) ASSESSMENT

Application Information		
NDA # 204242	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Zubsolv Established/Proper Name: : buprenorphine and naloxone Dosage Form: sublingual tablets Strengths: buprenorphine/naloxone 1.4 mg/0.36 mg <b>and</b> buprenorphine/naloxone 5.7 mg/1.4 mg		
Applicant: Orexo AB [Agent for Applicant: DJA Global Pharmaceuticals, Inc.]		
Date of Receipt: 9/6/2012		
PDUFA Goal Date: 7/6/2013		Action Goal Date (if different): 6/28/2013
Proposed Indication(s): maintenance treatment of opioid dependence		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Suboxone (buprenorphine and naloxone) sublingual tablet NDA 020733	Nearly all sections of labeling (i.e., sections 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17) include information by specific reference to Suboxone sublingual tablets.
Published literature 1) Stoller, KB, et al. Effects of buprenorphine/naloxone in opioid-dependent humans. <i>Psychopharmacology</i> (2001) 154:230–242. 2) Lanier, RK, et al. Physical dependence potential of daily tramadol dosing in humans. <i>Psychopharmacology</i> (2010) 211:457–466.	Cited literature supports the Sponsors contention that the lower doses of naloxone (vs the listed drug) are still effective in causing precipitated opioid withdrawal – the intended effect.

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Study OX219-003 was performed using the to-be-marketed formulation and Suboxone SL tablets, establishing the bridge to the listed drug.

**RELIANCE ON PUBLISHED LITERATURE**

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO

*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

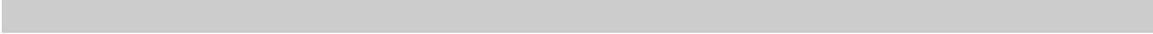
YES  NO

*If "NO", proceed to question #5.*

*If "YES", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Suboxone (buprenorphine /naloxone) sublingual tablets)	020733	Yes

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

Suboxone. Marketing ceased in March of 2013.

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Change in the ratio of buprenorphine:naloxone in each strength tablet.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

**Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES  NO   
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?  
YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES  NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

- Suboxone SL film (NDA 022410)
- Two approved ANDAs (203136 & 091422) to the listed drug, Suboxone SL tablets

**PATENT CERTIFICATION/STATEMENTS**

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification*

*was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

**Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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MATTHEW W SULLIVAN  
07/03/2013

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 204242  
Product Name: Zubsolv (buprenorphine and naloxone sublingual tablets)

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PMR/PMC Description: 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.

Submit the revised specifications as a Changes Being Effected (CBE-0) CMC Supplement.

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PMR/PMC Schedule Milestones: Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: 8/30/2013  
Other: \_\_\_\_\_ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Since the analytical method quantifies the impurities in the drug product they have to be robust in their validation. The proposed method for impurities in Naloxone lacks the typical accuracy and intermediate precision requirements of (b) (4) RSD. The impact of this is that Naloxone API related impurities in the drug product can potentially be overestimated or underestimated by (b) (4). Hence the applicant is being asked to optimize the analytical method to improve its accuracy and precision such that the method validation criteria of (b) (4) RSD are met. Because of the low level of impurities in the drug product, this is not considered a safety issue for approvability.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The study will optimize the analytical method for the quantification of Naloxone impurities in the drug product.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The applicant has agreed to revise and validate their analytical method for naloxone related impurities in the drug product to meet the accuracy and intermediate precision criteria of (b) (4) RSD.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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/s/  
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MATTHEW W SULLIVAN  
07/03/2013

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 204242  
Product Name: Zubsolv (buprenorphine and naloxone sublingual tablets)

PMR/PMC Description: A clinical trial to assess the risk of QT prolongation with Zubsolv sublingual tablet, i.e., a thorough QT (tQT) trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/30/2014</u>
	Study/Trial Completion:	<u>04/30/2015</u>
	Final Report Submission:	<u>01/31/2016</u>
	Other: <u>Draft Protocol Submission</u>	<u>11/30/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Available effective/viable treatments for opioid dependence are limited, and buprenorphine products provide a much needed viable option for this treatment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Information from a tQT study in NDA 21306 (Transdermal buprenorphine product for pain indication) suggested that buprenorphine at concentrations below what are likely to be achieved with Zubsolv tablets prolonged the QT interval (just exceeding the regulatory threshold for concern). This PMR will provide quantitative data with respect to QT prolongation potential with the use of Zubsolv tablets.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required clinical trial is a thorough QT clinical trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

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Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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/s/  
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MATTHEW W SULLIVAN  
07/03/2013

## SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

<b>Product Title</b>	<b>ZUBSOLV (buprenorphine and naloxone sublingual tablets) for sublingual administration CIII</b>
Applicant	Orexo AB
Application/Supplement Number	NDA 204242
Type of Application	Original
Indication(s)	For the maintenance treatment of opioid dependence
Established Pharmacologic Class <sup>1</sup>	Partial opioid agonist
Office/Division	ODE II/DAAAP
Division Project Manager	Matthew Sullivan
Date FDA Received Application	September 6, 2012
Goal Date	July 6, 2013
Date PI Received by SEALD	June 26, 2013
SEALD Review Date	June 28, 2013
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Division Director	Laurie Burke

PI = prescribing information

<sup>1</sup> The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

## Selected Requirements of Prescribing Information

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### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

**Comment:**

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

**Comment:** *HL is > ½ page. DAAAP will grant a waiver in the approval letter.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

**Comment:**

- YES** 4. White space must be present before each major heading in HL.

**Comment:**

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:** *The second and third statements under the Dosage and Administration header in Highlights do not reference the FPI. Include (2.1) after the second statement and (2.2) after the third statement. We recommend using bullets for each statement under the Dosage and Administration header in HL.*

*The statement under the Adverse Reactions header in Highlights does not reference the FPI. Include (6) at the end of the statement.*

## Selected Requirements of Prescribing Information

**YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

**YES** 7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES** 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

**NO** 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:** *The HL Limitation Statement is not on the line immediately beneath the HL heading. There is a space between the two. Delete the space.*

#### Product Title

**YES** 10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

**NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

## Selected Requirements of Prescribing Information

*Comment:* *The Initial U.S. Approval in HL is not placed immediately beneath the product title. There is a space between the two. Delete the space.*

### Boxed Warning

- N/A 12. All text must be **bolded**.

*Comment:*

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

*Comment:*

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

*Comment:*

N/A

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

*Comment:*

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

*Comment:*

### Recent Major Changes (RMC)

- N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

*Comment:*

N/A

18. Must be listed in the same order in HL as they appear in FPI.

*Comment:*

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

*Comment:*

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

*Comment:*

### Indications and Usage

## Selected Requirements of Prescribing Information

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

---

## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

## Selected Requirements of Prescribing Information

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- NO** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: Subsection heading 5.9 in the TOC reads as “Neonatal” but subsection heading 5.9 in the FPI reads as “Neonatal Abstinence Syndrome. The TOC subsection heading must match the FPI heading.

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

---

## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>

## Selected Requirements of Prescribing Information

<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- NO** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

**Comment:** In section 5.4 and 16, the cross reference to 17.2 should reference the section, not subsection heading (i.e., change to “[see Patient Counseling Information (17.2)]” instead of “[see Disposal of Unused ZUBSOLV Sublingual Tablets (17.2)]”).

In section 8.1, the first paragraph, the cross-reference “[see Animal Data]” does not reference a section or subsection heading. Change reference to include the correct section heading followed by the numerical identifier in italics.

In section 8.1, the fourth paragraph, the cross-reference “[See Warnings and Precautions]” does not include the numerical identifier and the entire contents are not in italics. Include the numerical identifier and italicize the entire contents.

## Selected Requirements of Prescribing Information

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

#### Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

#### Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

Comment: The clinical division will correct section heading 6.1 to read as “Clinical Trials Experience” instead of “Adverse Events in Clinical Trials-ZUBSOLV.”

- NO** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

## Selected Requirements of Prescribing Information

**Comment:** *The verbatim statement or appropriate modification that should precede the presentation of adverse reactions in the “Postmarketing Experience” subsection of Adverse Reactions is missing. Insert the statement or appropriate modification.*

*The clinical division will correct section heading 6.2 to read as “Postmarketing Experience” instead of “Adverse Events-Post-marketing Experience with buprenorphine/naloxone Sublingual Tablets.”*

### Patient Counseling Information

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

**YES**

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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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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ABIMBOLA O ADEBOWALE  
06/28/2013

ERIC R BRODSKY  
06/28/2013  
Eric Brodsky, labeling team leader, signing for Laurie Burke, SEALD Director

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: June 17, 2013

Reviewer: Vicky Borders-Hemphill, Pharm.D  
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, Pharm.D.  
Division of Medication Error Prevention and Analysis

Associate Director: Scott Dallas, RPh  
Division of Medication Error Prevention and Analysis

Drug Name(s): Zubsolv (Buprenorphine/Naloxone) Sublingual Tablets  
5.7/1.4 mg and 1.4/0.36 mg

Application Type/Number: NDA 204242

Applicant/sponsor: Orexo AB

OSE RCM #: 2013-880

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## 1 INTRODUCTION

This review evaluates the proposed container labels and carton and insert labeling for Zubsolv (buprenorphine/naloxone) sublingual tablets, NDA 204242, for areas of vulnerability that could lead to medication errors.

### 1.1 BACKGROUND

On September 6, 2012, Orexo AB submitted an NDA for Zubsolv (buprenorphine/naloxone) sublingual tablets.

### 1.2 PRODUCT INFORMATION

The following product information was provided in the insert labeling submitted April 8, 2013.

- Sponsor: Orexo AB
- Active Ingredients: buprenorphine/naloxone
- Indication of Use: for the maintenance treatment of opioid dependence
- Route of Administration: oral
- Dosage Form: sublingual tablet
- Strength: 5.7/1.4 mg (buprenorphine/naloxone), 1.4/0.36 mg (buprenorphine/naloxone) [ratio 4:1]
- Dose and Frequency:
  - One tablet sublingual daily
  - Target: 11.4 mg buprenorphine/2.8 mg naloxone per day (two 5.7/1.4 mg tablets).
  - Adjust: progressively in increments/decrements of 1.4 mg/0.36 mg or 2.8 mg/0.72 mg to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
  - Maintenance: range of 2.8 mg/0.72 mg to 17.1 mg/4.2 mg per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage
- How Supplied: outer carton containing 3 cards, each card contains a unit dose child resistant blister pack of 10 tablets (30 tablets)
- Storage: 20°C -25°C (68°F -77°F), with excursions permitted to 15 to 30°C (59-86°F) [see USP Controlled Room Temperature]
- Reference Listed Drug (RLD): Suboxone sublingual tablets (NDA 20733)

## 2 METHODS AND MATERIALS REVIEWED

### 2.1 PREVIOUS COMPLETED DMEPA REVIEWS

In OSE review # 2008-1807 dated July 1, 2009, DMEPA reviewed proposed container labels, carton and package insert labeling for Suboxone (buprenorphine/naloxone) sublingual film (FDA approved August 2010) and in that review used medication error cases related to Suboxone (buprenorphine/naloxone) sublingual tablets (NDA 20733) retrieved from FAERS to identify areas that could potentially contribute to Suboxone film medication errors.

In February 2013, DMEPA responded to a November 8, 2012 consult request from the Office of Regulatory Policy (ORP) to address issues raised in a citizen petition (CP) filed September 25, 2012 by Petitioner, Reckitt Benckiser (RB) regarding accidental pediatric exposures to buprenorphine-containing products. For this CP response, in OSE review # 2012-2635/TSI 437, DMEPA evaluated the trend in accidental pediatric exposures from year 2004 to year 2011 using data from National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES), Drug Abuse Warning Network (DAWN), Poison Control Center (PCC), and FDA Adverse Event Reporting System (FAERS) specifically comparing Suboxone tablet to Suboxone film. DMEPA also commented on the impact of educational intervention, the impact of packaging and dosage form on the rate of accidental pediatric exposure to buprenorphine-containing products specifically comparing Suboxone tablet to Suboxone film.

### 2.2 SELECTION OF MEDICATION ERROR CASES

For this review, DMEPA referred to medication errors related to Suboxone sublingual tablets (the RLD for this Application) that were identified in OSE review # 2008-1807 as a result of the AERS search conducted on February 1, 2009. We used the findings from review #2008-1807 as the labels, labeling, and packaging of Suboxone tablets have not significantly changed since the time of the previous review, and there were no other significant medication errors aside from pediatric exposures, which were evaluated in the response to the CP, that have arisen since that time. DMEPA also referred to the CP response in OSE review # 2012-2635/TSI 437 in order to provide consistent label and labeling recommendations for Zubsolv regarding accidental exposures and product packaging.

The search strategy employed in OSE review #2008-1807 is listed in Table 1 below.

**Table 1.**

<b>Search 1: AERS Search Strategy</b>	
<b>Date</b>	October 8, 2002 through February 1, 2009
<b>Drug Names</b>	Combination active ingredients: “bupren%” and “nalox%” Trade name: “Subo%” Verbatim: “subox%”
<b>MedDRA Search Strategy</b>	Medication Errors (HLGT) Pharmaceutical product complaint (PT)

Section 3 characterizes the errors identified in the previous reviews.

### **2.3 LABELS AND LABELING**

DMEPA reviewed the Zubsolv proposed container labels and carton and insert labeling submitted by the Sponsor on April 8, 2013, for risk of medication error and to identify areas of needed improvement.

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Current Container Labels (Appendix B)
- Current Carton Labeling (Appendix C)

## **3 MEDICATION ERROR RISK ASSESSMENT**

The following sections describe the risk assessment of Zubsolv labels and labeling.

### **3.1 MEDICATION ERRORS FOUND IN PREVIOUSLY COMPLETED DMEPA REVIEWS**

The AERS search conducted on February 1, 2009, in OSE review # 2008-1807, revealed several cases (n=13) associated with Suboxone tablets. Six of the thirteen cases involved unintentional exposure to infants and pediatric patients, three of the thirteen cases involved wrong route of administration, and four cases involved confusion of the Suboxone strengths.

#### **Pediatric exposure**

Six cases involved unintentional exposure to infants and pediatric patients. In all six cases children accidentally ingested Suboxone tablets. Root causes of the unintentional exposures were reported in 4 of the 6 cases. The reported cause in 3 cases was the child being left unattended with the medication, while the fourth case reported that the tablets were dropped on the floor. The child was found with the orange pill residue in the mouth and on the hands.

DMEPA's CP response (OSE review # 2012-2635/TSI 437) noted that many pediatric exposure cases to buprenorphine-containing products in FAERS, NEISS CADES, and the RADARS involved improper storage of buprenorphine products as a root cause. Additionally, DMEPA's evaluation of FAERS and NEISS CADES cases identified that some pediatric exposure cases reported the exposure to ½ tablets or film secondary to patients using less than a full tablet or film to achieve a dose (e.g. ½ of an 8mg tablet to achieve a 4 mg dose).

#### **Wrong Route**

Three cases involved wrong route of administration. One case described Suboxone tablets being crushed, then snorted, and soon afterwards the patient experienced withdrawal symptoms. The second case described a coroner's report of finding buprenorphine in the

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

decedent's stomach indicating that the patient either snorted or swallowed the tablets whole, but a definitive determination between the two routes could not be made. Causality was not reported and the reported outcome was death due to buprenorphine and diazepam toxicity. The third case described a patient intravenously injecting the medication intentionally. The outcome for this case was hospitalization.

### **Confusion with strength**

Other relevant cases to this review from the AERS search conducted on February 1, 2009, involved confusion between the Suboxone strengths (n=4). Two of these four cases were complaints about the presentation of the strength on Suboxone's labels. The first case indicated similar labels and lack of color differentiation as the source of confusion and the second case stated that the presentation of the strength was the source of the confusion because both labels have displayed '2 mg' on the front of the packaging which makes it confusing, and no strength appears immediately next to the brand name. The third and fourth cases involved the wrong strength of Suboxone being dispensed to patients. In both cases, the prescriber wrote a prescription for "Suboxone 2 mg". In each case, the pharmacist assumed the 2 mg was representative of the naloxone component in the higher strength tablet, instead of the buprenorphine component in the lower strength tablet. Causality was reported in both cases as the strength not being well differentiated on the label, an incomplete prescription, and a knowledge deficit that more than one strength existed.

## **3.2 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT**

### **Pediatric Exposure**

Unintentional exposures of infants and children to Suboxone sublingual tablets were due to improper storage and improper disposal of product (some secondary to partial tablets or films, or whole tablets being left on the floor). The proposed packaging for Zubsolv consists of a unit dose child resistant blister pack of 10 tablets per card with 3 cards per carton. This packaging is consistent with prior recommendations provided in OSE review # 2012-2635/TSI 437 (response to the CP for buprenorphine-containing products) regarding the use of unit-dose child resistant packaging for buprenorphine containing products to help mitigate pediatric exposure. The CP response acknowledges one of the main benefits of unit-dose packaging in terms of preventing pediatric poisoning is to limit the quantity of drug product that children access, thereby limiting the toxicity associated with accidental ingestions. Zubsolv proposed carton labeling includes the safe storage pediatric exposure statement similar to what is in the Suboxone Medication Guide and is consistent with the recommendation provided in the CP response. Thus, we find the proposed packaging of this product acceptable.

Additionally, according to FAERS and NEISS CADES cases identified in the CP response, some patients use less than a full tablet or film to achieve a dose (e.g. ½ of an 8mg tablet to achieve a 4 mg dose) and that in some cases the pediatric cases reported the exposure to ½ tablets or film of buprenorphine-containing products. AERS cases identified in OSE review # 2008-1807 indicated that unintentional pediatric exposure was also secondary to tablets being left on the floor. The CP response also found that some patients may be motivated to use partial amounts of a higher strength of a buprenorphine

containing product to achieve a given dose due to financial reasons or for dose adjustment due to clinical reasons, resulting in the practice of splitting tablets. The proposed Zubsolv sublingual tablets are not scored or designed to be split or cut. We therefore recommend that the proposed carton and insert labeling instruct patients not to use partial tablets by including the statement “Advise patients not to cut, chew, break or swallow Zubsolv sublingual tablet”. DMEPA acknowledges the statement in the insert labeling that instructs to dispose of unused tablets by flushing down the toilet and recommends that a similar statement be added to the carton labeling to make this statement readily visible to the consumer.

### **Wrong Route**

The wrong route of administration cases were related to the abuse and misuse of Suboxone tablets and the intentional consumption via the wrong route. All buprenorphine-containing products can be abused in a similar manner. Similar to Suboxone tablets, Zubsolv has language in the labeling to instruct prescribers about the abuse potential of this product. Zubsolv contains the active ingredient naloxone, an opioid receptor antagonist, to deter the use of this product via the intravenous or intranasal route.

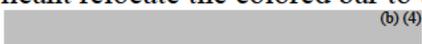
### **Confusion with strength**

Zubsolv contains two active ingredients and the strength of each active ingredient appears on the principal display panel of the labels and labeling (1.4 mg/0.36 mg and 5.7 mg/1.4 mg) as it does with the RLD, Suboxone.

The proposed labels submitted by the Applicant for Zubsolv attempt to differentiate the two product strengths by placing the strength statement in a colored box on the carton labeling. An orange colored box is used for the lower strength product (1.4 mg/0.36 mg) versus a purple colored box for the higher strength product (5.7 mg/1.4 mg). The colored boxes are located in the middle of the principal display panel, at the top of the back panel, and on the top panel of the carton labeling. The use of color differentiation and highlighting the strength of both active ingredients will help to minimize errors related to wrong strength selection.

However, there is another strength statement appearing on the principal display panel,

 (b) (4)

Additionally, there only needs to be one strength statement on the principal display panel. Having only one strength statement to appear on the principal display panel may reduce clutter and allow for other information on the carton to be more readily visible, and thus should be deleted. This strength statement is located in the customary position for the strength statement on the PDP, (directly beneath the established name), thus we will be requesting the Applicant relocate the colored bar to this customary location subsequent to the deletion  (b) (4). See Section 5.

Additionally, for each strength, the aforementioned colored boxes include the net quantity statement in close proximity to one of the presentations of the product strength. Product selection or dosing errors can occur if the net quantity statement is mistaken for

the product strength, leading to under- or over-dosing. The net quantity statement should appear on the principal display panel but away from the strength statement and not highlighted or boxed. Thus, we will recommend relocation of the net quantity statement for these labels.

Each strength of Zubsolv has a component which overlaps the opposite component in the other strength of the product (the lower strength formulation contains buprenorphine 1.4 mg and the higher strength formulation contains naloxone 1.4 mg). This overlap may cause confusion if prescribers do not specify the strengths of both components of the product on a prescription, since the 1.4 mg strength can refer to the buprenorphine or the naloxone component. Highlighting the strength of both active ingredients on the label and labeling is unlikely to impact the risk of prescribers specifying the strength of only one active ingredient of Zubsolv. Thus, there is still a risk that prescribers will only write the strength for one of the active ingredients of Zubsolv. This risk exists with the currently marketed product, Suboxone sublingual film (2mg/0.5mg and 8mg/2mg), and the introduction of Zubsolv sublingual tablets into the marketplace would not increase the risk of prescribers only writing the strength of one active ingredient.

Additionally, the risk of a prescriber only writing the strength of one active ingredient when ordering Zubsolv is likely minimized since Suboxone has been marketed since year 2002 and the film since year 2010, thus patients and healthcare providers are more familiar with the active ingredients of Suboxone and how to prescribe them. Furthermore, both of the previous cases that reported a medication error involving a prescription that only included a strength of one of the active ingredients of Suboxone tablets occurred within 2 years of the initial launch of Suboxone tablets. Therefore, we have no recommendations at this time regarding the strength statement of Zubsolv tablets, other than those recommendations mentioned above.

### **Insert labeling**

DMEPA provided recommendations for the insert labeling during labeling meetings with DAAAP.

## **4 CONCLUSIONS**

DMEPA concludes that the proposed container label and blister and carton labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of these products. We request the recommendations for the container labels in Section 5 be communicated to the Sponsor prior to approval.

## **5 RECOMMENDATIONS**

### **Comments to the Applicant**

DMEPA provides the following recommendations to be implemented prior to approval of the NDA:

#### **A. General Comment for all Labels and Labeling:**

1. The established name consists of the active ingredient and the dosage formulation. Ensure the established name appears as “buprenorphine and naloxone sublingual tablets”. Relocate the dosage form “sublingual tablets” to appear immediately

next to or below the active ingredients, but above the product strength, as the dosage form is a component of the established name statement. Revise the font of the dosage form to be of equal prominence with that of the active ingredients.

#### B. Blister

1. Replace the (b) (4) with a linear barcode.
2. (b) (4)
3. Revise the strength statement to appear after the revised established name (i.e., “buprenorphine and naloxone sublingual tablet 1.4 mg/0.36 mg”)
4. Relocate the proprietary name, established name, and strength to the top portion of the label above the lot and expiration statements.

#### C. Carton Labels

1. (b) (4)  
(b) (4) This color carton labeling.  
Ensure the strength is presented directly below the established name and not randomly presented on the labeling.
2. Revise the statement that reads (b) (4) to read “Do Not cut, crush, break, chew, or swallow tablet” on the back panel for consistency with the dosing instructions for this product.
3. Revise the statement that reads (b) (4) and “Do Not Cut, Crush, Break, Chew, or Swallow Tablet” to appear in title case on the principal display panel.
4. Add the following statement: “Discard unused tablets by immediately flushing down the toilet” on the back panel to be consistent with the insert labeling directions and to relay important information regarding proper disposal of unused product.
5. Relocate the scheduled drug designation (CIII) away from the active ingredients on the carton labeling. Ensure there is adequate white space between a revised established name and the CIII designation so that the CIII designation does not interfere with the readability of a revised established name. Ensure only one scheduled drug designation (CIII) appears on the panel. Any additional designations only add to clutter.
6. Reduce the size, relocate, or remove the graphic above the proprietary name as this presents as intervening matter which may distract from or distort important information.
7. As presented, the net quantity statement may be easily overlooked. Relocate the net quantity statement to the bottom third of the principal display panel and

appear away from the strength statement. Revise the net quantity statement so that it is not highlighted, or boxed.

8. (b) (4) Consider using only the text with the appropriate flavor (i.e., “menthol flavored”).

If you have further questions or need clarifications, please contact Vaishali Jarral, project manager, at 301-796-4248.

## APPENDICES

### APPENDIX A. DATABASE DESCRIPTIONS

#### FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/  
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BRENDA V BORDERS-HEMPHILL  
06/17/2013

JAMIE C WILKINS PARKER  
06/17/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

*Memorandum*

Date: June 11, 2013

To: Matthew Sullivan, Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)  
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 204242  
OPDP labeling comments for ZUBSOLV® (buprenorphine and naloxone)  
sublingual tablets for sublingual administration CIII  
Medication Guide

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OPDP has reviewed the Medication Guide (Med Guide) for ZUBSOLV® (buprenorphine and naloxone) sublingual tablets for sublingual administration CIII (Zubsolv) that was submitted for consult on November 16, 2012.

OPDP's comments on the proposed Medication Guide are based on the proposed draft marked version of the Medication Guide provided by Nathan Caulk (DMPP) on June 6, 2013. DMPP's review of the Medication Guide is being provided to the Review Division under separate cover.

OPDP has no comments on the proposed draft Medication Guide at this time.

Thank you for the opportunity to comment on these proposed materials.

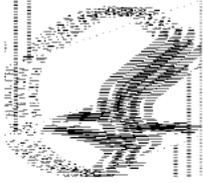
If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or [latoya.toombs@fda.hhs.gov](mailto:latoya.toombs@fda.hhs.gov).

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/s/  
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LATOYA S TOOMBS  
06/11/2013



Pediatric and Maternal Health Staff  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**PEDIATRIC AND MATERNAL HEALTH STAFF,  
MATERNAL HEALTH TEAM REVIEW**

**Date:** 06-07-2013

**From:** Leyla Sahin, M.D.  
Medical Officer,  
Pediatric and Maternal Health Staff, Maternal Health Team

**Through:** Melissa S Tassinari, PhD.  
Acting Team Leader,  
Pediatric and Maternal Health Staff, Maternal Health Team

**Through:** Lynne P Yao, M.D.  
Associate Director, Office of New Drugs  
Pediatric and Maternal Health Staff

**To:** Division of Anesthesia, Analgesia and Addiction Products

**Drug:** Zubsolv (buprenorphine-naloxone) sublingual tablet; NDA 204 442

**Applicant:** Orexo

**Subject:** Labeling for Pregnancy and Nursing Mothers

**Materials Reviewed:** Applicant labeling and justification document, literature review

**Consult Question:** Please review the proposed labeling for Pregnancy and Nursing Mothers

## **EXECUTIVE SUMMARY**

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.

## **INTRODUCTION**

Orexo Corporation submitted a 505(b)(2) application on January 3rd, 2013 for ZubSolv® (buprenorphine-naloxone) sublingual tablet for the maintenance treatment of opioid dependence. The referenced innovator drug, Suboxone®, was approved in 2002. The application was granted priority review due to its increased bioavailability compared to Suboxone, allowing for lower dosing. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Pediatric and Maternal Health Staff, Maternal Health Team's (PMHS-MHT) review of the applicant's proposed labeling for Pregnancy and Nursing Mothers. PMHS-MHT performed a literature review of buprenorphine and buprenorphine-naloxone use in pregnancy and breastfeeding. This review summarizes available data, and provides conclusions and recommendations regarding Pregnancy and Nursing Mothers labeling for ZubSolv.

## **BACKGROUND**

Buprenorphine is a partial mu-opioid agonist and kappa-antagonist that has a ceiling effect for respiratory depression. Subutex is the marketed name brand for buprenorphine alone, and Suboxone is the marketed combination of buprenorphine and naloxone, which was developed with the intent of deterring intravenous abuse of buprenorphine, as naloxone is inactive orally but results in opioid withdrawal if injected. Unlike the restrictive nature of outpatient methadone treatment, the ability of patients to be prescribed buprenorphine prescriptions by their physician improves access to care for patients and removes the social stigma of having to go to a clinic.

### **Opioid dependence and treatment during pregnancy**

Opioid dependence during pregnancy is a significant public health problem. Recent data from the 2010 National Survey on Drug Use and Health show that in the United States 4.4% of pregnant women (aged 15-44) reported use of illicit drugs.<sup>1</sup> Opioid dependence is associated

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<sup>1</sup> Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: summary of national findings. NSDUH Series H-41, HHS Publication No. (SMA) 11-4658. Rockville (MD): SAMHSA; 2011. Available at <http://www.oas.samhsa.gov/NSDUH/2k10NSDUH/2k10Results.pdf>.

with an increase in obstetrical complications such as low birth weight, preterm birth, and fetal death.<sup>2,3,4</sup> These effects may be related to the repeated exposure of the fetus to opioid withdrawal as well as the effects of opioid withdrawal on placental function. The rationale for maintenance treatment for opioid-dependence during pregnancy is to prevent complications of illicit opioid use and narcotic withdrawal, encourage prenatal care and drug treatment, reduce criminal activity, and avoid risks to the patient of associating with a drug culture. Historically, methadone has been the standard treatment for opioid dependence in pregnancy.<sup>4</sup> More recently, buprenorphine also has been administered to pregnant women as maintenance treatment for opioid-dependence, based on an accumulating body of medical literature. An American College of Obstetricians and Gynecologists' (ACOG) Committee Opinion states that buprenorphine may be offered to patients in need of opioid-assisted therapy during pregnancy.<sup>5</sup> Both ACOG and the Substance Abuse and Mental Health Services Administration (SAMSHA)<sup>4</sup> recommend the single-agent buprenorphine product during pregnancy to avoid any potential prenatal exposure to naloxone, especially if injected.

### **Neonatal Abstinence Syndrome**

All opiates that are used chronically during pregnancy, including methadone and buprenorphine use, can result in neonatal abstinence syndrome (NAS), which is characterized by hyperactivity of the central and autonomic nervous systems. Infants with neonatal abstinence syndrome may have uncoordinated sucking reflexes leading to poor feeding, become irritable, have diarrhea, and seizures.<sup>6</sup> The American Academy of Pediatrics considers neonatal abstinence syndrome as an expected and treatable condition that follows prenatal exposure to opioid agonists.<sup>6</sup>

## **REVIEW OF DATA**

### **I. Buprenorphine Use in Pregnancy Literature Review**

#### **A. Randomized controlled trials**

- 1. Jones HE, Kaltenschach K, Heil SH et al: Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure. *N Engl J Med* 2010; 363:2320-2331**

#### **Objective**

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<sup>2</sup> Minozzi S, Amato L, Vecchi S, Davoli M. Maintenance agonist treatments for opiate dependent pregnant women. *Cochrane Database of Systematic Reviews* 2008. Issue 2. Art.No.:CD006318. DOI:10.1002/14651858.CD006318.pub2

<sup>3</sup> Fajemirokun-Odudeyi O, Sinha C, Tutty S, Pairedeau P, Armstrong D, Phillips T, et al. Pregnancy outcome in women who use opiates. *Eur J Obstet Gynecol Reprod Biol* 2006; 126(2):170–5.

<sup>4</sup> Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. In: SAHMSA/CSAT treatment improvement protocols. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2008. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK26113>.

<sup>5</sup> American College of Obstetricians and Gynecologists Committee Opinion Opioid Abuse, Dependence, and Addiction in Pregnancy. Number 524, May 2012.

<sup>6</sup> American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. *Pediatrics* 2012; 129:e540-e560.

The objective of the study was to assess neonatal abstinence syndrome (NAS) in neonates exposed to buprenorphine compared to neonates exposed to methadone during pregnancy. Primary outcomes were the following:

1. number of neonates requiring treatment for NAS
2. the peak NAS score
3. the total amount of morphine needed to treat NAS
4. the length of the hospital stay for neonates
5. neonatal head circumference.

The seven secondary neonatal outcomes were the number of days during which medication was given for NAS, weight and length at birth, preterm birth (defined as birth at <37 weeks of gestation), gestational age at delivery, and 1-minute and 5-minute Apgar scores. The nine secondary maternal outcomes were cesarean section, weight gain, abnormal fetal presentation during delivery, anesthesia during delivery, the results of drug screening at delivery, medical complications at delivery, study discontinuation, amount of voucher money earned for drug-negative tests, and number of prenatal obstetrical visits.

### Methods

The authors conducted an eight site, international, double blinded, flexible dosing randomized controlled trial, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study. Between May 4, 2005, and October 31, 2008, opioid-dependent women between the ages of 18 and 41 years with a singleton pregnancy between 6 and 30 weeks of gestation (calculated on the basis of the last menstrual period and confirmed by ultrasonographic results) were screened and recruited. Women with disorders related to the use of benzodiazepines or alcohol were excluded from study participation.

Before randomization, all participants received rapid-release morphine sulfate as inpatients to achieve medical stabilization and to ease the transition to the double-blind medication. Participants were required to receive daily medications under observation in the study clinic. A blinded, individualized dosing schedule was used for the study medications, and a double-blind method was used to implement dose-unit increases or decreases (with dose adjustments of 2 mg for buprenorphine and 5 or 10 mg for methadone). Dose adjustment decisions were based on medication adherence, the participant's request, urine toxicologic results, and self-reported symptoms of withdrawal or craving. The study sites provided participants with comprehensive care. To promote drug abstinence, patients were given monetary vouchers in exchange for providing urine samples that were negative for opioids (other than buprenorphine and methadone), other illicit drugs, and misuse of prescription medications.

NAS assessment was performed in a blinded fashion using a predetermined scoring scale (modified Finnegan scale).

Covariates for the neonatal outcomes were: number of days of study medication; average daily number of cigarettes smoked during study enrollment; percent of cocaine-positive urine tests; exposure (yes vs. no) to selective serotonin reuptake inhibitor (SSRI) medications during study enrollment; number of prenatal obstetrical visits during study enrollment; and estimated gestational age at delivery (except when estimated gestational age at delivery was the outcome

measure). Maternal urine screening test results (positive v. negative) for opioids, benzodiazepines, cocaine, and marijuana in the 28 days prior to delivery were included as additional covariates for neonates treated for NAS, peak score on the MOTHER NAS scale during the assessment period, and days medicated for NAS.

### Results

A total of 16 of the 89 women in the methadone group (18%) and 28 of the 86 women in the buprenorphine group (33%) discontinued treatment before delivery ( $P=0.02$ ). Among the women who did not complete treatment, the mean number of days in the study was 35.1 (range, 4 to 155) for those in the methadone group and 8.6 (range, 0 to 80) for those in the buprenorphine group. “Dissatisfaction” with the study medication was reported as the reason for discontinuation by 71% of participants in the buprenorphine group, as compared with only 13% of those in the methadone group.

The study included 131 neonates whose mothers were followed to the end of pregnancy with 58 exposed to buprenorphine and 73 exposed to methadone.

The following statistically significant primary outcomes were seen:

1. neonates exposed to buprenorphine required 89% less morphine than did neonates exposed to methadone (mean total doses of 1.1 mg and 10.4 mg, respectively;  $P<0.0091$ )
2. neonates spent, on average, 43% less time in the hospital (10.0 vs. 17.5 days, respectively;  $P<0.0091$ ).

The following statistically significant secondary outcome was seen:

- neonates had a shorter duration of treatment for NAS (4.1 days vs. 9.9 days,  $P<0.003125$ ).

These differences remained significant when the analyses were adjusted for covariates. There were no significant differences between groups in other primary or secondary outcomes or in the rates of maternal or neonatal serious adverse events. Fifty seven percent of the methadone exposed infants required treatment for NAS compared to 47% of the buprenorphine exposed infants, which was not statistically different. The methadone group had a higher rate of nonserious maternal adverse events overall ( $P=0.003$ )

There were no significant between-group differences (including those who did not complete the study) in baseline characteristics, including measures of substance use.

The estimated gestational age at enrollment in the study was 18.7 weeks in both arms of the study.

### Authors’ Conclusions

The authors concluded that the benefits of buprenorphine in reducing the severity of NAS among neonates with this complication suggest that it should be considered a first-line treatment option in pregnancy.

#### Reviewer's Comments

*This study showed no difference between buprenorphine and methadone in the frequency of occurrence of NAS or in the peak severity of NAS. Statistically significant different outcomes were found in that the buprenorphine exposed neonates required less morphine, less days of treatment, and fewer days in the hospital. These differences in outcome cannot be explained by between-group differences such as severity of disease, as baseline characteristics, including participants who discontinued the study, were similar. One finding of the study is difficult to interpret is that no difference in NAS severity score between the buprenorphine and methadone arms was demonstrated; however, the buprenorphine exposed neonates required a lower mean total dose of morphine than the methadone exposed neonates (1.1 mg vs. 10.4 mg).*

*This trial was designed to assess NAS, not maternal outcomes, and is therefore limited in terms of utility in assessing buprenorphine's efficacy in pregnancy. The significantly greater proportion of women who discontinued buprenorphine (33% vs. 18% in the methadone arm) is an important limitation in terms of treatment efficacy. It is also concerning that 71% of participants in the buprenorphine group, as compared with only 13% of those in the methadone group discontinued treatment due to dissatisfaction.*

*Although there was no statistically significant difference in rates of drug use at delivery (15% in the methadone arm vs. 9% in the buprenorphine arm), there is no statistical analysis of abstinence rates during the course of pregnancy. There is information in the publication's Supplementary Appendix that shows that 33% of the participants (including those who did not complete the study) in the buprenorphine arm had a positive opioid positive screen during pregnancy compared with 23% in the methadone arm, and 21 % of the participants (including those who did not complete the study) in the buprenorphine arm had a cocaine positive screen, compared with 16% in the methadone arm. The higher rates of drug use in the buprenorphine arm raise concern regarding its efficacy compared to methadone.*

*Furthermore, the trial design is not reflective of real world conditions in that it excluded women who used benzodiazepines and alcohol; the study required daily visits, and provided comprehensive care and monetary incentives for remaining drug free.*

*This study did provide useful safety data that showed that there were no significant differences in maternal and neonatal adverse outcomes between the treatment groups, however the numbers are limited to 58 exposures in the buprenorphine group and 73 exposures in the methadone group. Although birth defects were not one of the study outcomes, they were included in the reporting of serious adverse events. The publication states that one infant in the methadone group had 2 surgeries for dextrocardia, and one infant in the buprenorphine group had renal failure and multiple surgeries. In assessing birth defects it is important to know the timing of exposure as the first trimester is of greatest concern in terms of organogenesis. The women in this study were enrolled at approximately 18.7 weeks of pregnancy in both study arms, and specific information on first trimester exposure is not provided. Although the publication states*

*that 47% of the participants in the methadone arm and 41% of the participants in the buprenorphine arm were treated with methadone or buprenorphine in the 30 days prior to the study, there is no data on exposures that occurred during the first trimester, therefore it is not possible to assess the risk for malformations.*

*Due to the limitations described above, it is difficult to draw definitive conclusions regarding buprenorphine's efficacy, and safety in terms of NAS and malformations.*

**2. Jones HE, Johnson RE, Jasinski DR, Milio L: Randomized controlled study transitioning opioid-dependent pregnant women from short-acting morphine to buprenorphine or methadone. Drug Alcohol Depend. 2005; 78: 33-8.**

The Pregnancy and Reduction of Opiates: Medication Intervention Safety and Efficacy (PROMISE) study was a small-scale, single-site randomized clinical trial conducted in the United States comparing buprenorphine to methadone that provided pilot data for the design of the MOTHER study. The nine women in the buprenorphine arm were approximately 22.8 weeks gestation, and the eleven women in the methadone arm were approximately 23.6 weeks gestation at enrollment in the study.

Similar to the MOTHER study, this study showed no difference between buprenorphine and methadone in the peak severity of NAS. Unlike the MOTHER study, this study showed a lower frequency of NAS that required treatment in the buprenorphine group compared to the methadone group, and it did not show a difference in the dose of morphine required to treat NAS. There was no correlation between dose of medication at delivery (for either buprenorphine or methadone) and intensity of NAS. Methadone and buprenorphine groups had similar rates of illicit opioid use during the study (15.6% and 16.7% respectively).

*Reviewer's Comments*

*No birth defects were noted in either arm of the study. As in the MOTHER study there is no information on exposures that occurred in the first trimester. The primary limitation of this study is the small sample size, which precludes the ability to draw any conclusions regarding the safety and efficacy of buprenorphine use in pregnancy.*

**3. Fischer G, Ortner R, Rohrmeister K: Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. Addiction. 2006; 101:275-81.**

This was a small-scale (included 8 women exposed to buprenorphine and 6 women exposed to methadone), single-site randomized clinical trial conducted in Austria comparing buprenorphine to methadone, that differed from the PROMISE study in that oxazepam as needed was included in the protocol. Women in the buprenorphine arm were approximately 24 weeks gestation, and women in the methadone arm were approximately 24.67 weeks gestation at enrollment in the study.

The methadone arm had significantly fewer urine samples positive for illicit opioids during the course of the study relative to the buprenorphine arm (4.35 vs. 35.26%). The mean duration of treatment for NAS in both the methadone and buprenorphine groups was similar (5 days). Five out of eight (63%) buprenorphine exposed neonates required treatment for NAS, compared to three out of six (50%) methadone exposed neonates. The total dose of morphine needed to manage NAS was similar in both groups (2 mg in the buprenorphine group vs. 2.7 mg in the methadone group). There was no correlation between the maternal dose of buprenorphine or methadone received and the severity of NAS.

There is no information on birth defects.

#### Reviewer's Comments

*Similar to the PROMISE study, this study is limited by the small sample size, which precludes the ability to draw any conclusions regarding the safety and efficacy of buprenorphine use in pregnancy.*

### **B. Prospective Observational Studies**

#### **1. Lejeune C, Dimmat-Durrand L, Gourarier L et al: Prospective multicenter observational study of 260 infants born to 259 opiate- dependent mothers on methadone or high-dose buprenorphine substitution. Drug Alcohol Depend. 2006; 82:250-7.**

This prospective, multicenter observational study in France included 159 women on buprenorphine maintenance during pregnancy and 100 women on methadone. In the buprenorphine exposed group 82% of the women had started taking the treatment prior to conception. There were no statistically significant differences between the two groups in terms of neonatal outcome including the following:

- NAS incidence that required treatment
- NAS severity
- duration of NAS treatment
- timing of NAS onset (37.5 hours for buprenorphine, 45 hours for methadone)
- duration of hospitalization
- low birth weight, head circumference, or prematurity.

There was no relationship between the dose of substitution agent and the severity of NAS. All newborns were discharged from the hospital.

#### Reviewer's Comments

*This study has the largest sample size of pregnant women exposed to buprenorphine, including at least 130 first trimester exposures. A limitation of this study is that although the authors state that all newborns were discharged from the hospital, they do not report on malformations.*

**2. Lacroix I, Berrebi A, Garipuy D, Schmitt L, Hammou Y, Chaumerliac C. et al. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective multicenter study. Eur J Clin Pharmacol 2011; 67: 1053–1059**

The objective of this prospective, multicenter observational study in France was to compare the perinatal morbidity and NAS of infants born to women taking methadone or buprenorphine during pregnancy. All buprenorphine exposures included first trimester exposures. The outcomes of the buprenorphine exposed group included 85 live births, 1 stillbirth (due to pre-eclampsia), 2 spontaneous abortions, 2 voluntary abortions, and 1 therapeutic abortion due to a fetus with multiple malformations (extremities and genitourinary system). The outcomes of the methadone exposed group included 40 live births, 2 stillbirths (1 in a woman who had a history of cocaine abuse, and 1 in a fetus with achondroplasia), 1 spontaneous abortion, 1 voluntary abortion, and 1 therapeutic abortion because the woman had HIV. There were no statistically significant differences between the two groups in terms of NAS incidence, birth weight, body length, or prematurity. The only statistically significant difference in outcome between the two groups was related to need for treatment of NAS as 80% of methadone exposed neonates required treatment vs. 57% of buprenorphine exposed neonates ( $P=0.03$ ). A mean onset time of NAS of approximately 2 days was similar for both groups (ranging from a few hours to 8 days).

**3. Kahila H, Saisto, T et al.: A prospective study on buprenorphine use during pregnancy: effects on maternal and neonatal outcome. Acta Obstet Gynecol Scand. 2007; 86:185-90.**

This prospective observational study was conducted in Finland to assess neonatal outcomes following in utero exposure to buprenorphine, compared to the country's background rates. Sixty seven pregnancies of 66 buprenorphine users were followed prospectively in an outpatient multidisciplinary antenatal setting by an obstetrician, a midwife, a psychiatric nurse and a social worker. Thirty eight women were enrolled in the study before 15 weeks gestation, and 13 women were enrolled after 24 weeks gestation (information is not provided for the remaining 16 patients). Infant birth weight, length, head circumference, Apgar scores, umbilical artery pH, urine samples for toxicological screening, malformations, occurrence of NAS and medication for NAS were recorded. The only statistically significant finding was that buprenorphine exposed neonates had lower birth weight than the national average (3180 g vs. 3512 g,  $p<0.001$ ). The pregnancies and deliveries of buprenorphine-using women were uneventful, but 76% of neonates had NAS, and 57% needed morphine replacement therapy.

**4. Kakko J, Heilig M, Sarman I: Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. Drug Alcohol Depend. 2008, Jul 1; 96(1-2):69-78**

A population based comparison of 47 consecutive, prospectively followed buprenorphine-exposed pregnancies in Stockholm County, Sweden, to 35 retrospectively analyzed consecutive methadone-exposed pregnancies. Twenty seven women started buprenorphine before conception and were exposed during the entire pregnancy, and 7 women started buprenorphine in the first trimester. One woman started buprenorphine at 37 weeks gestation. There were no infants with malformations. There were statistically significant differences with buprenorphine compared to methadone treatment: higher birth weight (3,250 g vs. 2,941 g,  $P=0.008$ ), lower incidence of

NAS (19% vs. 28%,  $P=0.0008$ ), lower incidence of NAS that required pharmacological treatment (14.9% vs. 52.8%), and shorter hospital stay (9.4 days vs. 19.7 days). The authors comment that the difference in length of substance use (1 year for buprenorphine vs. 4 years for methadone) and the severity of the drug dependence may have contributed to the observed differences in outcomes.

**5. Brulet C, Chanal C, Ravel P, Mazurier E, Boulot P, Faucherre V. Multidisciplinary monitoring and psychosocial support reduce complications of opiate dependence in pregnant women: 114 pregnancies. Presse Med. 2007 Nov; 36 (11 Pt 1):1571-80.**

This prospective observational study conducted in France followed outcomes in 48 pregnant women treated with buprenorphine and 26 pregnant women who were treated with methadone. There is no information on the timing of exposure during pregnancy. Among the buprenorphine exposed newborns 72.9 % had NAS, and 80.8% of methadone exposed newborns had NAS (no statistical analysis was done). There was no correlation between the need for treatment of NAS and dose of buprenorphine or methadone. The buprenorphine exposed patients had less preterm births and low birth weight infants (8.3% and 23.6% respectively) than the methadone exposed patients (12.5% and 46.2%). All infants were reported as normal and discharged home.

**6. Welle-Strand GK, Skurtveit S, Jones HE, Waal H, Bakstad B, Bjarkø L, Ravndal E. Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009.**

This mixed prospective-retrospective study compared neonatal outcomes following prenatal exposure to either methadone ( $n=90$ ) or buprenorphine ( $n=49$ ) in a national clinical cohort in Norway from 1996 to 2009. The incidence of NAS treatment (only unadjusted data presented: 60 % for methadone vs. 58% for buprenorphine), duration of treatment of NAS (only unadjusted data presented: 38.6 days for methadone vs. 27.7 days for buprenorphine), and the peak NAS score did not differ between methadone and buprenorphine exposed newborns. After adjusting for relevant covariates, the only statistically significant difference was that buprenorphine-exposed newborns had larger head circumferences (34.7 cm vs. 33.7,  $P=0.02$ ) compared to methadone exposed newborns. All women were exposed in the first trimester. The buprenorphine exposed neonates had 2 malformations: 1 neural tube defect and 1 case of gastroschisis. The methadone exposed neonates did not have any malformations.

Reviewer's Comments

*Based on the prospective observational studies reviewed, it is not possible to clearly conclude that buprenorphine is associated with a less severe NAS than methadone as reported in the MOTHER study, The results are conflicting and it is difficult to make comparisons across studies due to the variations in study design such as outcome assessments, blinding of assessors, adjustments for covariates, etc. Concomitant maternal exposure to benzodiazepines and SSRIs will affect the severity and duration of NAS. The incidence of buprenorphine associated NAS that requires treatment is widely variable, and this is probably due to the effect of concomitant exposures to SSRIs and benzodiazepines. The severity of NAS does not seem to correlate with the maternal dose (see Table 2 in Appendix A).*

*It is also not possible to draw conclusions regarding other safety outcomes such as preterm birth, low birth weight, and head circumference as not all studies evaluated these outcomes, and there were differences in other concomitant exposures, severity of addiction, etc. None of the studies were designed with malformations as the primary outcome, but several do report on timing of exposure and malformations. As seen in Table 1, which summarizes the published studies, the cumulative published data provide information on approximately 300 first trimester exposures, which did not detect a safety signal.*

*In addition to the above prospective studies, a number of smaller sample size studies and case series on buprenorphine exposure in pregnancy report some safety data, which are generally unremarkable, and do not indicate a safety signal in terms of birth defects or adverse perinatal outcomes. A recent review<sup>7</sup> conducted by the primary investigator of the MOTHER study, reviewed the published literature on buprenorphine use in pregnancy, including 44 non-randomized studies (i.e. prospective studies, case reports and series and retrospective chart reviews), of which 28 involve independent samples. The percentage of neonates treated for NAS in the non-randomized studies varied between 0 and 100%, with an unweighted mean of 48%. Unweighted means for estimated gestational age (14 studies: 39.0 weeks), weight (20 studies: 3087.2 g), length (10 studies: 49.4 cm) and head circumference (nine studies: 34.0 cm), extracted from all such studies that reported summary data, suggest that most neonates were full term and within normal limits.*

*The table below is a summary of the published studies on buprenorphine use in pregnancy.*

**Table 1. Summary of Published Studies on Buprenorphine Use in Pregnancy**

<b>Randomized Controlled Trial</b>	<b>Buprenorphine N (number)</b>	<b>Estimated Gestational Age at enrollment (weeks)</b>	<b>Methadone N (number)</b>	<b>Estimated Gestational Age at enrollment (weeks)</b>
<i>MOTHER 2010 Jones, USA</i>	58	18.7	73	18.7
<i>PROMISE 2005 Jones, USA</i>	9	22.8	11	23.6
<i>Fischer 2006 Austria</i>	8	24	6	24.67

<sup>7</sup> Jones H, Heil S, et al. Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review. *Addiction* 2012; 107:5-27.

**Table 1. Summary of Published Studies on Buprenorphine Use in Pregnancy (continued)**

<b>Prospective Observational Studies</b>	<b>Buprenorphine N (number)</b>	<b>Estimated Gestational Age at enrollment (weeks)</b>	<b>Methadone N (number)</b>	<b>Estimated Gestational Age at enrollment (weeks)</b>
<i>Lejeune 2006 France</i>	159 (approx. 130 first trimester exposures)	82% before pregnancy	101	72% before pregnancy
<i>Lacroix 2011 France</i>	85	All first trimester exposures	40	All first trimester exposures
<i>Kahila 2007 Finland</i>	67	38 enrolled before 15 weeks 15 enrolled after 24 weeks No info on 16 patients	0	
<i>Brulet 2007 France</i>	48	No info	26	No info
<i>Kakko 2008 Sweden</i>	47	34 exposed in first trimester	35	31 exposed in first trimester
<i>Welle-Strand 2013 Norway cohort study (mixed retrospective, prospective)</i>	49	All first trimester exposures	90	All first trimester exposures

Total number of first trimester exposures: at least 298  
130 Lejeune, 85 Lacroix, unknown Kahila, unknown Brulet, 34 Kakko, and 49 Welle-Strand

## **II. Buprenorphine-naloxone Use in Pregnancy Literature Review**

### **Retrospective Chart Review**

#### **1. Debelak K, Morrone WR, O'Grady KE, Jones HE. Am J Addict. 2013 May;22(3):252-4. Buprenorphine + Naloxone in the Treatment of Opioid Dependence during Pregnancy-Initial Patient Care and Outcome Data.**

The authors conducted a retrospective chart review of 10 women who were treated with buprenorphine-naloxone during pregnancy. Seven maternal outcome measures were assessed: weight gain, fetal presentation at delivery, cesarean delivery, analgesia during delivery, urine drug screening results at delivery, number of days of maternal hospital stay, and initiation of breastfeeding following delivery. Eleven neonatal outcome measures were assessed: gestational age at delivery, 1 and 5 minute Apgar scores, head circumference, length, and weight at birth, treatment for NAS, total amount of morphine sulfate needed to treat NAS, length of hospital stay for NAS treatment, and length of hospital stay.

Maternal findings were unremarkable. Eight out of ten neonates were full-term; all 10 had normal birth parameters. Four neonates were treated for NAS, and the mean neonatal hospital stay was 10 days; these were consistent with values reported in the literature for the

buprenorphine only product. The amount of morphine required to treat NAS (3.5 mg) was higher than the amount required in the MOTHER trial (1.1 mg). There is no information on timing of exposure or on birth defects.

#### Reviewer's Comments

*This study is limited by the small sample size, which precludes the ability to draw any conclusions regarding the safety and efficacy of buprenorphine use in pregnancy.*

### **III. Lactation Literature Review**

Based on limited data from a study of 6 lactating women<sup>8</sup> who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and (b) (4) mg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose. Buprenorphine was undetectable (<187 ng/L) in the urine of 3 infants; the other 3 had urine concentrations of about 468 ng/L. A 9-month-old breastfed infant whose mother was taking 20 mg (0.32 mg/kg) of buprenorphine daily had serum and urine collected. Serum concentrations of buprenorphine and norbuprenorphine were 234 ng/L and 745 ng/L, respectively, at 2.25 hours after the previous maternal dose. A urine sample obtained 3.5 hours after the previous maternal dose contained <234 ng/L and 455 ng/L of the drug and metabolite, respectively. Norbuprenorphine urine concentrations ranged from 414 to 1987 ng/L (median 952 ng/L). Follow up assessment of infants was performed one month later and all were normal.

Based on limited data from a study of 7 lactating women<sup>9</sup> who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose.

#### Reviewer's Comments

*Based on these published lactation studies, buprenorphine's estimated infant daily dose is substantially less than the limit of 10% of the maternal weight adjusted dose that is cited in a published reference regarding the use of drugs in breastfeeding.<sup>10</sup> In addition, naloxone is not orally bioavailable, therefore is not expected to be of concern to the breastfeeding infant.*

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<sup>8</sup> Lindemalm S, Nydert P, Svensson JO et al. Transfer of buprenorphine into breast milk and calculation of infant drug dose. J Hum Lact. 2009; 25:199-205.

<sup>9</sup> Ilett KF, Hackett LP, Gower S et al. Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk during maternal buprenorphine substitution treatment. Breastfeed Med. 2012; 7:269-74.

<sup>10</sup> Hale T. Medications and Mothers' Milk. 2012. Fifteenth Edition.

*No serious adverse reactions have been reported in the literature. A literature review by the Substance Abuse and Mental Health Services Administration (SAMSHA)<sup>11</sup> of approximately 40-50 women who were on buprenorphine maintenance during pregnancy and following delivery who breastfed their newborn infant showed that breastfeeding did not suppress NAS.*

*The National Library of Medicine's Lactmed review<sup>12</sup> states that "because of the low levels of buprenorphine in breast milk, its poor oral bioavailability in infants, and the low drug concentrations found in the serum and urine of breastfed infants, its use is acceptable in nursing mothers." Both ACOG<sup>5</sup> and the Substance Abuse and Mental Health Services Administration (SAMSHA)<sup>4</sup> recommend breastfeeding for mothers taking buprenorphine.*

## **LABELING**

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers labeling information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the labeling, not the amount.

The innovator drug, Suboxone, which is the reference drug for this 505 (b)(2) application, is labeled pregnancy category C based on adverse developmental effects in the rat and rabbit at exposures similar to the recommended human dose. There is no human data in Suboxone labeling. The applicant reviewed the medical literature on the use of buprenorphine and buprenorphine/naloxone during pregnancy and lactation and proposed the addition of published data to the Nursing Mothers subsection of labeling. Because the medical literature on use of buprenorphine is predominantly based on buprenorphine, rather than the combination buprenorphine-naloxone, the applicant proposed to not include any human data on buprenorphine. See Appendix B for applicant's proposed labeling.

### *Reviewer's Comments*

*PMHS-MHT disagrees with the applicant's rationale regarding not adding data on the use of buprenorphine during pregnancy to Zubsolv labeling, as buprenorphine is the active ingredient. Naloxone, as the abuse deterrent, is not absorbed orally and therefore not expected to result in*

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<sup>11</sup> CSAT (Center for Substance Abuse Treatment). Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004a.

<sup>12</sup> toxnet.nlm.nih.gov

*fetal exposure if used as labeled. Information from published data that can inform risk-benefit considerations on use of buprenorphine in pregnant women should be added to labeling.*

## **DISCUSSION AND CONCLUSIONS**

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 NAS outcomes in 58 buprenorphine exposed women vs. 73 methadone exposed women (the MOTHER study), two small pilot RCTs, several published prospective observational studies, and case series and reports. The MOTHER study showed that buprenorphine exposed neonates required less morphine, fewer days of treatment, and fewer days in the hospital. However, the trial was designed to assess NAS, not maternal outcomes; and therefore, is of limited utility in assessing buprenorphine's efficacy in treatment of opioid dependence in pregnancy. The significantly greater proportion of women who discontinued buprenorphine (33% vs. 18% in the methadone arm) is an important limitation in terms of treatment efficacy. It is also concerning that 71% of participants in the buprenorphine group, as compared with only 13% of those in the methadone group discontinued treatment due to dissatisfaction. Furthermore, the trial design is not reflective of other existing comorbidities in that it excluded women who used benzodiazepines and alcohol; the study required daily visits, and provided comprehensive care and monetary incentives for remaining drug free.

Based on the cumulative published data, it is not possible to clearly conclude that buprenorphine is associated with a less severe NAS than methadone as seen in the MOTHER study, as the results are conflicting and it is difficult to make comparisons across studies due to the variations in study design such as outcome assessments, blinding of assessors, adjustments for covariates, etc. The incidence of buprenorphine-associated NAS that requires treatment is widely variable, and this is probably due to the effect of concomitant exposures to SSRIs and benzodiazepines. However in most studies the severity of NAS does not seem to correlate with the maternal dose.

The cumulative published data do not identify safety signals in terms of maternal or birth outcomes. The studies were not designed to assess malformations, however several studies do report on gestational timing of exposure and malformations. Available published data on at least 300 first trimester buprenorphine exposures have not shown an increase in fetal malformations. The published data on buprenorphine-naloxone exposure in pregnancy is limited to one chart review of 10 women; however naloxone is not orally absorbed, and therefore is not expected to result in exposure to the fetus, if taken as labeled. New information from published data on the consequences for newborns of use of this product in pregnant women should be added to labeling. Additionally, new information that should be added to pregnancy labeling include that available published data have shown no increase in incidence of malformations, and that there does not appear to be a dose response relationship between the maternal buprenorphine dose and the incidence of neonatal abstinence syndrome.

PMHS-MHT had several discussions with DAAAP regarding the published data. In concurrence with DAAAP, PMHS-MHT agrees that the current regulatory language under Pregnancy,

“ZUBSOLV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus” adequately reflects the risk –benefit profile regarding use in pregnancy. In addition, PMHS-MHT had several discussions with DAAAP’s Toxicology reviewers, Dr. Dan Mellon and Dr. Elizabeth Bolan regarding the reproductive developmental toxicology data in an effort to summarize the nonclinical data in labeling in a manner that is clinically relevant to health care providers. They were limited in their ability to review and revise the extensive nonclinical data due to the regulatory limitations of this 505 (b)(2) application, however, there may opportunity to do so if there are future supplements submitted by the innovator.

New information from published data that can inform risk-benefit considerations on use of buprenorphine in lactating women should also be added to labeling. Based on two published lactation studies, buprenorphine’s estimated infant dose is substantially less than the limit of 10% of the maternal weight adjusted dose that is the standard reference regarding the use of drugs in breastfeeding. In addition, naloxone is not orally bioavailable, therefore is not expected to be of concern to the breastfeeding infant. No serious adverse reactions have been reported in the literature related to breastfeeding. Useful information that should be added to lactation labeling include that available published data have shown that buprenorphine is present in very low levels in breast milk and that available data have not shown adverse reactions in breastfeeding infants.

## **RECOMMENDATIONS**

1. Add information on published pregnancy data to labeling (see Appendix C).
2. Add information on published lactation data to labeling (see Appendix C).

**APPENDIX A**

**Table 2. Summary of NAS Outcomes in Published Studies on Buprenorphine Use in Pregnancy**

RCT	Buprenorphine						Methadone					
	NAS Rate %	NAS Tx Rate	NAS peak	Hosp Days	Tx days	MS dose	NAS Rate %	NAS Tx Rate	NAS peak	Hosp Days	Tx days	MS dose
MOTHE R 2010 Jones, USA		47 =	=	10 <		1.1 <		57 =	=	17.5 >		10.4 >
PROMI SE 2005 Jones, USA		22 <	=			2 =		46 >	=			2.7 =
Fischer 2006 Austria		63 >			5.3 =	2 =		50 <			4.8 =	2.7 =

APPENDIX A

**Table 2. Summary of NAS Outcomes in Published Studies on Buprenorphine Use in Pregnancy (continued)**

Prosp Obser Study  +other findings	Buprenorphine						Methadone					
	NA S Rate  %	NAS Tx Rate	NAS peak	Hosp Days	Tx days	MS dose	NAS Rate  %	NAS Tx Rate	NAS peak	Hosp Days	Tx days	MS dose
<i>Lejeune 2006</i>		49 =	=		16 =			52 =	=		18 =	
<i>Lacroix 2011</i>	=	57 <					=	80 >				
<i>Kahila 2007 Finland *</i>	76	57										
<i>Brulet 2007 France **</i>	72.9						80.8					
<i>Kakko 2008 Sweden ***</i>	40.4 <	14.9 <		9.4 <			77.8 <	52.8 >		19.7 >		
<i>Welle-Strand 2013 Norway cohort study (mixed retrospective, prospective) ****</i>		58 =	=		27.7 =			60 =	=		38.6 =	

RCT=Randomized Controlled Trial; Bup=Buprenorphine; N=number; Rate=percent of newborns that required treatment for NAS; Tx=treatment; peak=measure of severity; Hosp= Hospital; M= Methadone; MS=morphine sulfate; Diff=difference; dose is in mg; ==no difference between buprenorphine exposed and methadone exposed group; <=less than; >=greater than; \* Lower birth weight compared to national average; \*\* buprenorphine group had lower incidence of preterm birth and low birth weight compared to methadone group;\*\*\* buprenorphine group had higher birth weight than methadone group; \*\*\*\*buprenorphine group had larger head circumference than methadone group

**APPENDIX B**  
**Applicant's proposed labeling**

The following is the applicant's proposed labeling for ZubSolv:

-----WARNINGS AND PRECAUTIONS-----

- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (b) (4)

-----USE IN SPECIFIC POPULATIONS-----

(b) (4)

**5 WARNINGS AND PRECAUTIONS**

**5.9 Neonatal Withdrawal**

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus, and there have been reports of convulsions, apnea, respiratory depression, and bradycardia.

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

Pregnancy Category C.

There are no adequate and well-controlled studies of ZUBSOLV sublingual tablets or buprenorphine/naloxone in pregnant women. ZUBSOLV sublingual tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(b) (4)

**Teratogenic Effects:**

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 11.4 mg on a mg/m<sup>2</sup> basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 11.4 mg on a mg/m<sup>2</sup> basis). Acephalus was observed in one rabbit fetus

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06/07/2013

MELISSA S TASSINARI  
06/09/2013

LYNNE P YAO  
06/10/2013

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: June 7, 2013

To: Bob A. Rappaport, MD  
Director  
**Division of Anesthesia, Analgesia, and Addiction  
Products (DAAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): ZUBSOLV (buprenorphine and naloxone)

Dosage Form and Route: sublingual tablets

Application Type/Number: NDA 204242

Applicant: Orexo AB c/o DJA Global Pharmaceuticals, Inc.

## 1 INTRODUCTION

On September 6, 2012, Orexo AB c/o DJA Global Pharmaceuticals, Inc. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 204242 for ZUBSOLV (buprenorphine and naloxone) sublingual tablets with the proposed indication for the maintenance treatment of opioid dependence. The Reference Listed Drug (RLD) is SUBOXONE (buprenorphine and naloxone) sublingual tablets which was originally approved on October 8, 2002 and discontinued by Ricketts Benckiser Pharmaceuticals Inc. on March 18, 2013.

On November 27, 2012, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for ZUBSOLV (buprenorphine and naloxone) sublingual tablets.

This review is written in response to a request by DAAAP for DMPP to review the Applicant's proposed Medication Guide (MG) for ZUBSOLV (buprenorphine and naloxone) sublingual tablets.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

## 2 MATERIAL REVIEWED

- Draft ZUBSOLV (buprenorphine and naloxone) sublingual tablets MG received on September 6, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on May 22, 2013.
- Draft ZUBSOLV (buprenorphine and naloxone) sublingual tablets Prescribing Information (PI) received on September 6, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on May 22, 2013.
- Approved SUBOXONE (buprenorphine and naloxone) sublingual tablets comparator labeling dated December 22, 2011.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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NATHAN P CAULK  
06/07/2013

BARBARA A FULLER  
06/07/2013

LASHAWN M GRIFFITHS  
06/07/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

*Memorandum*

Date: June 6, 2013

To: Matthew Sullivan, Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)  
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 204242  
OPDP labeling comments for ZUBSOLV® (buprenorphine and naloxone)  
sublingual tablets for sublingual administration CIII  
Labeling Review

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OPDP has reviewed the proposed package insert (PI) for ZUBSOLV® (buprenorphine and naloxone) sublingual tablets for sublingual administration CIII (Zubsolv) that was submitted for consult on November 16, 2012. Comments on the proposed PI are based on the version sent via email from Matthew Sullivan (RPM) on May 22, 2013 entitled "draft-labeling-text.doc".

Comments regarding the PI are provided on the marked version below.

Thank you for the opportunity to comment.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or [latoya.toombs@fda.hhs.gov](mailto:latoya.toombs@fda.hhs.gov).

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LATOYA S TOOMBS  
06/06/2013

## Sullivan, Matthew

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**From:** Sullivan, Matthew  
**Sent:** Thursday, June 06, 2013 8:51 AM  
**To:** Damaris DeGraft-Johnson (ddj@djaglobalpharma.com)  
**Subject:** Carton labeling 204242

Damaris –

We will have additional comments on the carton labeling soon, but I do have one that I can share with you at the moment.

1. [Provide updated blister card label to include dosage form "sublingual tablets".](#)

In this case, and with the upcoming comments on the outer cartons, we'd like to see a new PDF showing this 'mockup.' You should email it to us for an initial review, and then subsequently submit it to the NDA as usual.

Thanks,  
Matt

---

Matthew W. Sullivan, M.S.  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Food and Drug Administration  
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MATTHEW W SULLIVAN  
06/06/2013

**MEMORANDUM**

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

DATE: May 30, 2013

TO: Bob A. Rappaport, M.D.  
Director, Division of Anesthesia, Analgesia, and  
Addiction Products

FROM: Young Moon Choi, Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 204-242, buprenorphine  
and naloxone (OX219), sponsored by Orexo AB, Sweden

At the request of the Division of Anesthesia, Analgesia, and  
Addiction Products (DAAAP), the Division of Bioequivalence and  
GLP Compliance (DBGLPC) conducted audits of the clinical and  
analytical portions of the following bioequivalence study:

**Study Number:** OX210-003 (Novum # 11160501)  
**Study Title:** "An open-label, fasting, randomized, two- period  
crossover, comparative bioavailability study in  
healthy volunteers to assess the  
pharmacokinetics, tolerability and safety of  
OX219 sublingual tablet compared to Suboxone®  
sublingual tablet under naltrexone block"

The FDA audit of the analytical portion of the above study was  
conducted at (b) (4)

(b) (4) (b) (4)  
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(b) (4) (b) (4)  
(b) (4) (b) (4)

. The FDA

was conducted at Novum Pharmaceutical Research Services, Las Vegas, NV (March 7 - March 22, 2013) by ORA investigator, Anthony E. Keller.

The audits included a thorough examination of study records, facilities and equipment, and interviews and discussions with the firm's management and staff.

Following inspection of the analytical portion of the study, no significant objectionable conditions were observed at the analytical site and no Form FDA-483 was issued; however, Form FDA-483 was issued (Attachment 1) at Novum Pharmaceutical Research Services for observations pertaining to the clinical portion of the study. The Form FDA-483 observations, Novum's response (Attachment 2) and DBGLPC's evaluation of the observation follow:

(b) (4)

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/s/  
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YOUNG M CHOI  
05/31/2013

SAM H HAIDAR  
05/31/2013

WILLIAM H TAYLOR  
05/31/2013



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** May 13, 2013

**To:** Bob Rappaport, MD, Director  
 Division of Analgesics, Anesthesia, and Addiction Products (DAAAP)

**Through:** Michael Klein, PhD, Director  
 Controlled Substance Staff

**From:** Stephen Sun, MD, Medical Officer  
 Controlled Substance Staff

**Subject:** **Topic:**  
 Abuse Potential Assessment of New Drug Application

**Application:**  
 NDA 204242 (OX219; buprenorphine / naloxone)  
 [Previously: IND110637 (OX219; buprenorphine / naloxone)]  
 5.7 mg buprenorphine/1.4 mg naloxone sublingual tablet  
 1.4 mg buprenorphine/0.36 mg naloxone sublingual tablet

**Proposed Indication:**  
 Maintenance treatment of opioid dependence

**Sponsor:**  
 Orexo AB

- Materials reviewed:**
- Orexo AB. OX219 (buprenorphine and naloxone) sublingual tablets. IND110637. Pre-NDA Face-to-face meeting background package. Type B meeting. Submission Date: June 4, 2012. Meeting date: July 17, 2012.
  - Orexo AB. Report 10 3299. Naloxone extraction in small volumes from OX 219 low strength sublingual tablets.
  - Inwegen RV, Katz NP. Qualitative systematic review of the minimum effective dose of naloxone to precipitate withdrawal in persons physically dependent on opioids. Aug 8, 2012.

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## I. Summary

### A. Background:

This memorandum is in response to a CSS consult dated October 9, 2012, from the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) pertaining to NDA204242 (reference: IND110637) for buprenorphine and naloxone combination tablet proposed for the management of opioid dependence submitted by Orexo AB. In addition to requesting CSS participation in internal and industry meetings, the consult involves a review of the New Drug Application.

In a pre-IND meeting held on February 3, 2011, FDA and Sponsor agreed that the amount of naloxone released from their low-dose product under conditions of misuse is sufficient to precipitate an aversive reaction in individuals dependent on full agonists, either from convincing evidence from literature, or from clinical pharmacology study/studies to be conducted by or for the Sponsor. The Sponsor has subsequently submitted two sources of information to address this, including: (a) extraction study using the lower strength of OX219 and (b) a systematic literature review to assess the current consensus on the minimum amount of naloxone needed to induce withdrawal. The conclusions are based upon the review of these elements and additional abuse-related sections within the application.

### B. Conclusions:

1. The following are the abuse-related product highlights:
  - a) OX219 is a combination buprenorphine/naloxone sublingual tablet that is being proposed for the maintenance treatment of opioid dependence and being submitted as a 505(b)(2) application. Buprenorphine is a known DEA schedule III substance whereas naloxone is a non-scheduled substance. Product will therefore remain as a Schedule III product similar to the reference listed drug.
  - b) Schedule III products with buprenorphine (and naloxone) that are used for treatment of opioid dependence can be used in office-based opioid treatment as a form of substitution therapy. Since buprenorphine is a C-III scheduled substance with abuse potential, safeguards to mitigate risks of its misuse, abuse, addiction, diversion, and overdose should remain in place.

- c) The pharmacokinetic profile of the product and the extent of patient drug exposure is relatively similar to Suboxone (based on PK studies OX219-003 and OX219-004); therefore, the abuse-related risk profile will likely be similar to the reference listed drug.
- d) Sponsor provided results from an in vitro extraction study of OX219 (Report 10 3299) under the following 8 conditions: (b) (4)  
[REDACTED]  
[REDACTED]  
In all conditions at 1, 5, and 10 min time points, the ratio of 4:1 (buprenorphine: naloxone) was not exceeded suggesting that the minimum ratio was maintained when dissolved. Buprenorphine does not appear to be preferentially extracted.
- e) Sponsor provided a systematic literature review (Inwegen and Katz, 2012) to justify that (b) (4) dose of naloxone sufficiently precipitates withdrawal in individuals physically dependent on full  $\mu$ -opioid agonists. Findings include:
- i. Ten studies showed statistically significant precipitation of withdrawal due to parenteral (IV, IM, and SC) naloxone doses  $\leq 0.2$  mg when maintained on methadone (9 studies) and morphine (1 study).
  - ii. Two studies did not show consistent withdrawal effects of intramuscular 0.25 mg naloxone, but concluded as lack of sufficient physical dependence with one author suggesting a reflection of low levels of dependence and the second potentially a result of using a weak mu-opioid agonist, i.e. tramadol.
  - iii. When buprenorphine was co-administered with naloxone, buprenorphine did not prevent the precipitation of withdrawal but the perceived “liking” of buprenorphine was reduced.
- f) Sponsor has submitted a Risk Evaluation and Mitigation Strategy (REMS) similar to the current reference listed drug to be evaluated by the Division of Risk Management. At present, there is a class-wide REMS that applies to all buprenorphine-containing, oral transmucosal products indicated for the treatment of opioid dependence known as the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS. A primary goal of the BTOD REMS is to mitigate the risks of accidental overdose, misuse, and abuse.
2. The proposed OX219 formulation is not an abuse-deterrent formulation based upon the current science and the Sponsor has not requested additional language than what is available in the currently marketed formulation. Therefore, the language proposed for the product label on the risks of abuse and dependence would be similar to the

existing marketed buprenorphine and naloxone combination that does not include explicit abuse-deterrent claims. The Sponsor's in vitro studies are not adequate for any additional language to be added to the label.

3. Single-entity buprenorphine formulations are available as DEA Schedule III marketed, generic products for the treatment of opioid dependence. Therefore, additional evaluation for the product's abuse potential is not warranted at this time for the following reasons:
  - a) The result of purification or differential separation of buprenorphine from the combination tablet is similar to acquiring existing, currently available single-entity buprenorphine formulations
  - b) The target population of this product are patients with diagnosed opioid dependence who are known to be high-risk opioid abusers
  - c) Tampering with a rapidly-dissolving, sublingual tablet formulation to accelerate the drug release rate would offer little benefit
  - d) Sponsor seeks no additional claim as an abuse-deterrent opioid product.

However, data from any additional abuse-related studies will further enhance the product's science.

4. If the Sponsor seeks claims in the future that the formulation deters buprenorphine abuse, Sponsor should reference the January 2013 FDA Draft Guidance for Industry – Abuse-Deterrent Opioids – Evaluation and Labeling.<sup>1</sup> A comprehensive evaluation of its abuse deterrent features would include the following depending on the proposed claims (Sponsor may request a separate meeting):
  - a) Provide a comprehensive review of postmarketing surveillance data on the current known methods of buprenorphine and naloxone misuse, abuse, and diversion
  - b) Conduct a comprehensive evaluation of the formulation in a variety of temperatures, pH's, and polarity conditions using a wide range of environments and solvents to simulate an abuser's approach to differentially purify the opioid (buprenorphine) from the antagonist (naloxone)
  - c) Conduct a comprehensive evaluation of the formulation that simulates abusers' approaches for intravenous, insufflation, and inhalation abuse
  - d) Conduct human abuse potential studies of intact and manipulated formulation using various routes
  - e) Evaluation of long-term postmarketing surveillance data that shows the formulation mitigates abuse

---

<sup>1</sup> FDA. Draft Guidance - Guidance for Industry – Abuse-Deterrent Opioids – Evaluation and Labeling. Jan 2013.

### **C. Recommendations to the Division:**

1. Sponsor needs to inform the Drug Enforcement Administration of their intent to manufacture this buprenorphine (and naloxone) formulation for the purposes of requesting any drug quantity needs that may be limited by quotas.
2. Sponsor should minimize the risks of misuse, abuse, addiction, diversion, and overdose throughout the product life cycle.
3. Sponsor should provide detailed narratives on misuse, abuse, addiction, diversion, and overdose in the submission of post-approval periodic safety reports, particularly focusing on identifying new methods of tampering of this formulation.

## **II. Discussion**

OX219 is a combination buprenorphine/naloxone sublingual tablet that is being proposed for the maintenance treatment of opioid dependence and being submitted as a 505(b)(2) application. Buprenorphine is a known schedule III substance under the CSA, whereas naloxone is a non-scheduled substance. Sponsor is presently not requesting an abuse-deterrent claim but will need to justify the inclusion of naloxone in the formulation and its ability to release if inappropriately used for intravenous abuse based on prior discussions with the review division.

### **A. Chemistry:**

1. Buprenorphine is a semi-synthetic opioid and is a well-characterized Schedule III controlled substance. Buprenorphine is a long-acting analgesic with approximately 20 - 50 times the analgesic potency of morphine and is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone, a non-scheduled substance, is an antagonist at mu-opioid receptors and produces opioid withdrawal when administered parenterally in individuals physically dependent on full opioid agonists.
2. Orexo proposes OX219, a sublingual buprenorphine and naloxone tablet formulation for the treatment of opioid dependence, in a 4:1 ratio. Naloxone is included in the formulation purportedly to deter the intravenous abuse of buprenorphine. The Reference Listed Product (RLD) includes a sublingual tablet and a sublingual film that have been marketed under the name of Suboxone<sup>®</sup> (NDA 020733 and NDA 022410, respectively). As noted in pre-IND meetings, Sponsor was informed that they needed to demonstrate that the amount of naloxone released from the low-dose product (OX219), would be sufficient to precipitate an aversive reaction to individuals dependent on full mu-agonists.

3. The two proposed strengths of OX219 are 5.7 mg buprenorphine/1.4 mg naloxone and a 1.4 mg buprenorphine/0.36 mg naloxone but are intended to provide similar bioavailability and pharmacokinetic profiles as the reference listed product (Suboxone®). The recommended target dose of OX219 is 11.4 mg/2.8 mg buprenorphine/naloxone / day (two 5.7/1.4 mg tablets) as a single daily dose. The dosage is titrated in increments and decrements of 1.4 mg/0.36 mg or 2.8 mg/0.72 mg buprenorphine/naloxone. The maintenance dose is intended to be in the range of 2.8 mg/0.72 mg to 17.1 mg/4.2 mg buprenorphine/naloxone per day depending on the individual patient.

4.



5. H

environmental conditions would need to be examined as part of a comprehensive evaluation of the formulation:

- a) To evaluate differential solubility (under static and agitated conditions):
  - i. Varied pH conditions (room and elevated temperatures), e.g. acetic acid, hydrochloric acid, ammonium hydroxide, sodium bicarbonate, trisodium phosphate
  - ii. Varied polar conditions (room and elevated temperatures), e.g. acetone, ethyl acetate, methylene chloride, toluene, methanol, isopropyl alcohol, and chloroform
  - iii. Varied temperature conditions, e.g. to enhance the solubility of the active in different solvents
- b) To evaluate intranasal abuse potential, a method to characterize pulverization or other method for insufflation would need to be explored
- c) To evaluate differential vaporization (inhalation abuse potential), a method to exploit the differentials of the melting point between the two actives would need

to be explored, e.g. buprenorphine melting point: 272°C whereas naloxone melting: 200°C

- d) To evaluate intravenous abuse potential, a method to prepare the formulation into a solution suitable for intravenous injection, including small volume solubility (1, 2, 5 mL) with and without reconstitution in a solution suitable for injection, would need to be explored

## B. Pharmacology of drug substance and active metabolites:

1. No self-administration, conditioned-place preference, drug discrimination, psychomotor, or physical dependence studies were provided by the Sponsor. As a 505(b)(2), Sponsor references the RLD as the basis for abuse-related evaluation.

## C. Clinical Pharmacology:

1. The underlying pharmacology is a high absorption profile of a lesser starting amount of buprenorphine and naloxone in OX219 than found in the RLD but the plasma concentrations of buprenorphine are similar with a reduced exposure to naloxone. The highest strength of the OX219 sublingual tablet contains 5.7 mg buprenorphine and 1.4 mg naloxone, and has been shown to achieve plasma concentrations of buprenorphine that are similar to the RLD containing 8 mg of buprenorphine and 2 mg of naloxone. In addition, a lower strength sublingual OX219 tablet has also been formulated for the purpose of titration and contains 1.4 mg buprenorphine and 0.36 mg naloxone, which corresponds to the 2/0.5 mg strength of the RLD. The pharmacokinetic profile for OX219-4 based on the results from Study OX219-003 (Table 1).

**Table 1:** Pharmacokinetic Profile of OX219-4 and RLD (Suboxone<sup>®</sup>) from Study OX219-003

	<b>OX219-004 (5.7/1.4)</b>	<b>Suboxone<sup>®</sup> (8/2)</b>
<b>Buprenorphine</b>		
AUC <sub>inf</sub> [h x ng/mL]	26.1(9.7)	29.9 (10.6)
C <sub>max</sub> [ng/mL]	3.0 (1.1)	3.1 (1.2)
T <sub>max</sub> [h]	1.75 (0.7; 4.0)	1.75 (0.7; 4.0)
T <sub>1/2</sub> [h]	25.9 (9.8)	25.2 (9.3)
<b>Naloxone</b>		
AUC <sub>inf</sub> [h x pg/mL]	636.9 (391.4)	722.5 (309.2)
C <sub>max</sub> [pg/mL]	261.7 (209.1)	273.1 (171.3)
T <sub>max</sub> [h]	0.8 (0.3; 1.5)	0.8 (0.3; 2.5)
T <sub>1/2</sub> [h]	7.2 (6.1)	8.8 (6.1)
<b>Norbuprenorphine</b>		
AUC <sub>inf</sub> [h x ng/mL]	32.8 (17.8)	44.6 (23.3)

Cmax [ng/mL]	0.9 (0.5)	1.1 (0.6)
Tmax [h]	1.0 (0.5; 72.0)	1.5 (0.7; 48.0)
T1/2 [h]	32.5 (10.4)	40.5 (30.0)

2. All four OX219 clinical pharmacology studies (Study OX219-001: Comparative bioavailability study of an early OX219 formulation; Study OX219-002: Comparative bioavailability study using formulation OX219-3; Study OX219-003: Comparative bioavailability study using formulation OX219-4; Study OX219-004: Dose proportionality study using the formulation OX219-4) were conducted under a naloxone block and in healthy subjects.
  - a) Adverse event profiles of treatment-related, abuse-related adverse events as noted in the safety population (all four clinical pharmacology studies) showed that OX219 (N=298) versus Suboxone (N=100) had less asthenia (0.0% vs. 3.0%), fatigue (3.7% vs. 5.0%), feeling hot (1.0% vs. 2.0%), somnolence (4.4% vs. 7.0%), euphoric mood (1.3% v. 3.0%), flushing (0.7% vs. 1.0%) but more decreased appetite (5.7% vs. 0.0%), hyperhidrosis (1.0% vs. 0.0%). In general, the adverse event profiles of OX219 were similar to the RLD with the exception of a decreased appetite noted in the OX219 formulation.
  - b) Study withdrawals of subjects were a result of non-abuse related adverse events. No withdrawal or dependence, overdose, or intentional misuse cases were reported.

#### D. Clinical Studies:

1. No human abuse potential studies were provided by the Sponsor. As a 505(b)(2), Sponsor uses the RLD as the basis for abuse-related evaluation of buprenorphine.
2. No clinical efficacy and safety studies have been performed for OX219. Sponsor intends to reference human efficacy and safety data from the RLD.

#### E. Integrated Assessment:

##### 1. Postmarketing Experience - Review of Literature

- a) Sponsor provided a systematic review of the literature as justification that the lowest dose of OX219 contains a sufficient quantity of naloxone ( (b) (4) ) to deter parenteral abuse (Inwegen and Katz, 2012) by precipitated withdrawal in individuals physically dependent on full  $\mu$ -opioid agonists. The summary is as follows:

- i. 10 studies showed statistically significant precipitation of withdrawal due to parenteral (IV, IM, and SC) naloxone doses  $\leq 0.2$  mg when maintained on methadone (9 studies) and morphine (1 study).
- ii. 2 studies did not show consistent withdrawal effects of intramuscular 0.25 mg naloxone but concluded as lack of sufficient physical dependence with one author suggesting a reflection of low levels of dependence and the second potentially a result of using a weak mu-opioid agonist, i.e. tramadol.
- iii. When buprenorphine was co-administered with naloxone, buprenorphine did not prevent the precipitation of withdrawal but the perceived “liking” of buprenorphine was reduced.

## 2. Misuse, Abuse, and Diversion

- a) As a Schedule III buprenorphine product proposed for the treatment of opioid dependence, the Sponsor will need to meet the requirements for both the Controlled Substances Act and the Drug Addiction Treatment Act. Training of healthcare professionals in compliance with both laws are operationally outlined in the REMS.
- b) A Risk Evaluation and Mitigation Strategy (REMS) for OX219/Zubsolv has been included with three goals: (1) Mitigate the risks of accidental overdose, diversion, misuse, and abuse, (2) Ensure patients are appropriately informed of the serious risks associated with use, and (3) Minimize risk associated with unintended pediatric exposure. Submission is to be evaluated by OSE’s Division of Risk Management. As of February 22, 2013, a class-wide REMS was approved for all transmucosal buprenorphine products indicated for opioid dependence; the Sponsor should seek to participate in the collaboration or operate a similar program to mitigate such risks.
- c) (Johanson et al., 2012) As part of a quarterly physician survey (N=8,194 surveys completed) as a postmarketing surveillance study by the Sponsor of the RLD, buprenorphine/naloxone diversion and abuse increased from 2005 to 2009 (as a result of increased prescribing), 46% of physicians believed that drug was diverted but 44% believed illegal use was for self-management of withdrawal, followed by maintenance until entering treatment (34%), trying its effects (17%), and to get high (7%). Additionally, 53% of physician surveys believed the source was from substance abuse patients.
- d) According to a recent review of buprenorphine by the Office of Surveillance and Epidemiology, there were approximately (b) (4) dispensed prescriptions of

oral buprenorphine-containing products for 1 million patients during year 2012; an estimated (b) (4) % of patients were prescribed buprenorphine products intended for opioid dependence management<sup>2</sup>.

- e) According to recent statistics, “The estimated number of emergency department visits in which buprenorphine was involved as either a direct cause or a contributing factor increased from 3,161 in 2005 to 30,135 in 2010, according to a recently released report from the Substance Abuse and Mental Health Services Administration (SAMHSA). More than half (52%) of these buprenorphine-related emergency department (ED) visits were for the nonmedical use of pharmaceuticals” (University of Maryland, 2013)<sup>3</sup>. During this time period from 2005 to 2010, there had also been the introduction of a buprenorphine/naloxone combination that may affect the interpretation of the results.

### 3. Potential Evaluation as an Abuse-Deterrent Opioid Formulation

- a) Single-entity buprenorphine formulations are currently available as DEA schedule III products and exist as marketed generic products for the treatment of opioid dependence registered under ANDA090360, ANDA090622, and ANDA078633. Therefore, additional evaluation for the product’s abuse potential is not warranted at this time since the result of purification or differential separation of buprenorphine from the combination tablet is similar to acquiring existing single-entity buprenorphine formulations, the target population of this product are patients with diagnosed opioid dependence who are known to be high abuser risks, and Sponsor seeks no additional claim as an abuse deterrent opioid product.
- b) Furthermore, additional studies to examine the formulation under physical manipulation of a rapidly dissolving sublingual product are unlikely to accelerate an already rapid release of the active ingredient of the intact formulation. Therefore, while the submitted extraction studies are basic, additional studies would not affect the approvability of this product based upon this application but would help to understand more of the product science.
- c) However, if the Sponsor seeks any future claims on the abuse deterrent features of the formulations, the January 2013 FDA Draft Guidance for Industry – Abuse-Deterrent Opioids – Evaluation and Labeling would provide a framework for the types of studies that are required based upon the types of claims that are sought. In such instances, the Sponsor may request a separate meeting to discuss a study planning. Some of the requirements include the following:

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<sup>2</sup> Food and Drug Administration. Psychopharmacologic Drugs Advisory Committee Meeting - March 21, 2013. Probuphine (buprenorphine hydrochloride subdermal implant). Briefing materials.

<sup>3</sup> University of Maryland. Number of U.S. emergency department visits involving buprenorphine increases nearly ten-fold from 2005 to 2010. CESAR Fax. February 4, 2013. 22(5).

- i. Provide a review of postmarketing surveillance data on the current known methods of buprenorphine and naloxone misuse, abuse, and diversion
- ii. Conduct a comprehensive evaluation of the formulation in a variety of temperatures, pH's, and polarity conditions using a wide range of environments and solvents to simulate an abuser's approach to differentially purify the opioid (buprenorphine) from the antagonist (naloxone); some of these studies are defined in the above 'Chemistry' section
- iii. Conduct a comprehensive evaluation of the formulation that simulates an abusers' approach for intravenous, insufflation, and inhalation abuse
- iv. Conduct human abuse potential studies of intact and manipulated formulation using various routes
- v. Evaluation of postmarketing surveillance data that shows the formulation mitigates abuse

#### **4. Labeling:**

- a) The labeling language for this proposed formulation in 9.0 Drug Abuse and Dependence section would likely be similar to the RLD. Sponsor is proposing that the product labeling will be similar to the RLD.

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/s/  
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STEPHEN W SUN  
05/13/2013

MICHAEL KLEIN  
05/13/2013

## Sullivan, Matthew

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**From:** Sullivan, Matthew  
**Sent:** Friday, April 19, 2013 4:05 PM  
**To:** Damaris DeGraft-Johnson (ddj@djaglobalpharma.com)  
**Cc:** Aaron R. Truesdale (art@djaglobalpharma.com)  
**Subject:** pH and temperature, NDA 204242

Damaris –

We are increasingly aware of the need to provide labeling information about the effects of temperature and pH on bioavailability for drugs that are delivered transmucosally. If you have any information about the effects of temperature or pH on transmucosal bioavailability of buprenorphine in general, or your product specifically, please provide it, and propose wording for labeling to reflect that information. If no information is available, provide proposed labeling reflecting this.

Thanks,  
Matt

---

Matthew W. Sullivan, M.S.  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia,  
and Addiction Products  
Food and Drug Administration  
Phone 301-796-1245  
Fax 301-796-9723  
[matthew.sullivan@fda.hhs.gov](mailto:matthew.sullivan@fda.hhs.gov)

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/s/  
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MATTHEW W SULLIVAN  
04/26/2013

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 204242 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Zubsolv [proposed] Established/Proper Name: buprenorphine and naloxone sublingual tablets Dosage Form: SL tablets Strengths: buprenorphine/naloxone 1.4 mg/0.36 mg <b>and</b> buprenorphine/naloxone 5.7 mg/1.4 mg		
Applicant: Orexo AB Agent for Applicant (if applicable): DJA Global Pharmaceuticals, Inc.		
Date of Application: Sep 5, 2012 Date of Receipt: Sep 6, 2012 Date clock started after UN:		
PDUFA Goal Date: Jul 6, 2012		Action Goal Date (if different):
Filing Date: Nov 5, 2012		Date of Filing Meeting: Nov 2, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5 - New Formulation or New Manufacturer		
Proposed indication(s)/Proposed change(s): Maintenance treatment of opioid dependence		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):				
List referenced IND Number(s): 110637				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?  <i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>22410</td> <td>Suboxone SL Film</td> <td>NDF</td> <td>Aug 30, 2013</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	22410	Suboxone SL Film	NDF	Aug 30, 2013									<p>X</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
22410	Suboxone SL Film	NDF	Aug 30, 2013																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>		<p>X</p>		<p>The referenced product – NDA 020733 – previously had 7</p>																

				years of orphan exclusivity, which expired in 2009.
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>		X		
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index</b> : Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>				
<b>Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			<b>X</b>	
<ul style="list-style-type: none"> <li>If yes, were all of them submitted on time?</li> </ul>			<b>X</b>	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			<b>X</b>	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			<b>X</b>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and	X			

(3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i> Oct 9, 2012	X			

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
<b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b>	X			
<b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b>  <i>If no, request in 74-day letter</i>	X			
<b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</b>  <i>If no, request in 74-day letter</i>	X			
<b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b><u>Proprietary Name</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		Submitted to IND 110637
<b><u>REMS</u></b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	X			
<b><u>Prescription Labeling</u></b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide)			

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>		X		No EOP2 meeting, but PIND Meeting held Feb 3, 2011.
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> Jul 17, 2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** Nov 2, 2012

**BLA/NDA/Supp #:** 204242

**PROPRIETARY NAME:** Zubsolv [proposed]

**ESTABLISHED/PROPER NAME:** buprenorphine and naloxone sublingual tablets

**DOSAGE FORM/STRENGTH:** SL tablets

**APPLICANT:** Orexo AB

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Maintenance treatment of opioid dependence

**BACKGROUND:** 505(b)(2) submission, referencing NDA 020733, Suboxone SL tablets. The proposed NDA differs from the referenced product only in the ratio of the active ingredients to one another.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matt Sullivan	Y
	CPMS/TL:	Sara Stradley	N
Cross-Discipline Team Leader (CDTL)	Celia Winchell		Y
Clinical	Reviewer:	Pam Horn	Y
	TL:	Celia Winchell	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Wei Qiu	Y
	TL:	Yun Xu	N
Biostatistics	Reviewer:	David Petullo	Y
	TL:	Dionne Price	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Julia Pinto	Y
	TL:	Prasad Peri	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Stephen Sun	Y
	TL:	Mike Klein	N
Other reviewers	Akm Khairuzzaman ONDQA Biopharmaceutics		Y
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b> No clinical studies performed</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b>  It was noted at the filing meeting that the Sponsor had not yet submitted certain datasets as requested by the Clin Pharm review team. The Sponsor was reminded that these data were necessary for filing, and subsequently submitted the files on Nov 5, 2012.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> No biostatistics review necessary, per Dionne Price, as no clinical efficacy submitted or performed.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL</b></p>	<input type="checkbox"/> Not Applicable

<p><b>(PHARMACOLOGY/TOXICOLOGY)</b></p>  <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
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<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Bob Rappaport  <b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): n/a  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day</li> </ul>

	<p>filing letter; For NDAs/NDA supplements: see CST for choices)</p> <ul style="list-style-type: none"> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:  <a href="http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f">http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f</a> ]</p>
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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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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MATTHEW W SULLIVAN  
11/16/2012

# **REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION**

**Application:** 204242

**Application Type:** New NDA

**Name of Drug:** OX219 (buprenorphine and naloxone) sublingual tablets.

**Applicant:** Orexo AB (c/o DJA Global Pharmaceuticals, Inc.)

**Submission Date:** September 5, 2012

**Receipt Date:** September 6, 2012

## **1.0 Regulatory History and Applicant's Main Proposals**

This 505(b)(2) NDA provides for a buprenorphine and naloxone SL tablet. The application references NDA 020733 Suboxone (buprenorphine and naloxone) SL tablets. (The ratio of the buprenorphine:naloxone is slightly different when compared with the listed product.)

## **2.0 Review of the Prescribing Information (PI)**

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## **3.0 Conclusions/Recommendations**

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

As the deficiencies were minor, they will not be communicated to the Sponsor at this time, but rather included in the "working" version of the PI.

## Selected Requirements of Prescribing Information (SRPI)

### 5.0 Appendix

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## Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

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### Highlights (HL)

#### GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

## Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

**Comment:**

**YES**

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a Boxed Warning is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

**Comment:**

**YES**

7. A horizontal line must separate HL and Table of Contents (TOC).

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

**YES**

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:**

#### Highlights Limitation Statement

**YES**

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

**Comment:**

#### Product Title

**YES**

10. Product title in HL must be **bolded**.

**Comment:**

#### Initial U.S. Approval

**YES**

## Selected Requirements of Prescribing Information (SRPI)

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

### Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

### Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

### Indications and Usage

YES

## Selected Requirements of Prescribing Information (SRPI)

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

### Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

### Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

### Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

### Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

### Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

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## Contents: Table of Contents (TOC)

### GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

## Selected Requirements of Prescribing Information (SRPI)

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

- YES** 34. When a section or subsection is omitted, the numbering does not change.

Comment:

- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

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## Full Prescribing Information (FPI)

### GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

- YES** 37. All section and subsection headings and numbers must be **bolded**.

Comment:

- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

<b>Boxed Warning</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>

## Selected Requirements of Prescribing Information (SRPI)

<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

**Comment:**

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

**Comment:**

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### Boxed Warning

- N/A** 42. All text is **bolded**.

**Comment:**

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

**Comment:**

## Selected Requirements of Prescribing Information (SRPI)

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

**Comment:**

### Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

**Comment:**

### Adverse Reactions

- NO** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”*

**Comment:**

- NO** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

*“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”*

**Comment:**

### Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

**Comment:**

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/s/  
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MATTHEW W SULLIVAN  
11/16/2012