

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204242Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesia, Analgesia, and Rheumatology Products

NDA/BLA #s: 204242
Products: Zubsolv (buprenorphine and naloxone) sublingual tablets
SPONSOR: Orexo
FROM: Judith A. Racoosin, MD, MPH
DATE: June 17, 2013

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

Since Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone) sublingual tablets were approved on October 8, 2002, we have become aware of data showing an increase in misuse and abuse of these products, as well as reports of children accidentally exposed to Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone). Reports from postmarketing surveillance reveal an upward trend in indices of extent of abuse of Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone) as noted in interviews of patients entering substance abuse treatment. Additionally, the reports show that there is an illegal trade in buprenorphine products which involves patients selling, bartering, or giving away their own prescribed medications to friends. The reports also show that prescribing practices by some physicians contribute to the availability of buprenorphine for abuse and misuse. Furthermore, a CDC report¹ published in January 2013 showed a disproportionate number of emergency department visits and hospitalizations due to pediatric accidental exposures to Subutex (buprenorphine) and Suboxone (buprenorphine/naloxone). In 2009 buprenorphine products accounted for only 2.2% of retail opioid prescriptions, but Suboxone accounted for 9.5% of emergent hospitalizations for drug ingestion by children aged <6. We considered this information to be “new safety

¹ Emergency Department Visits and Hospitalizations for Buprenorphine Ingestion by Children — United States, 2010–2011. *Morbidity and Mortality Weekly Report* 2013; 16(3): 56.

information” as defined in the Food and Drug Administration Amendments Act of 2007 (FDAAA).

A REMS for Suboxone (buprenorphine/naloxone) film was approved in August 2010. A REMS for Suboxone (buprenorphine/naloxone) and Subutex (buprenorphine) tablets was approved in December 2011. The BTOD (Buprenorphine for the Treatment of Opioid Dependence) REMS was approved in February 2013 for generic oral transmucosal buprenorphine products.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Zubsolv (buprenorphine and naloxone), a 505(b)(2) NDA, that is a buprenorphine and naloxone sublingual tablet to ensure the benefits of Zubsolv (buprenorphine and naloxone) outweigh their (1) risks of exposure to Zubsolv (buprenorphine and naloxone) in persons for whom it was not prescribed, including accidental exposure in children and (2) risks of abuse and misuse. In reaching this determination, we considered the following:

- A. Zubsolv is indicated for the treatment of opioid dependence. The estimated number of patients in the United States classified with dependence on or abuse of pain relievers is 1.7 million persons and over 200,000 were classified with dependence on or abuse of heroin. This estimate is based the 2007 National Survey on Drug Use and Health.²
- B. Opioid dependence is a serious and life-threatening condition associated with morbidity and mortality due to overdose, blood-borne and sexually-transmitted diseases, and a variety of psychosocial consequences.
- C. Zubsolv is effective in the treatment of opioid dependence as measured by improvements in drug use behavior and retention in treatment.
- D. Treatment with Zubsolv may continue indefinitely.
- E. Zubsolv is associated with adverse events including abuse and accidental overdose leading to potentially lethal respiratory depression, hepatotoxicity, allergic reactions, and accidental pediatric exposures which are potentially lethal. Abuse and accidental overdose are common in the population, as are hepatic events attributable to blood-borne illnesses and use of other hepatotoxic substances.

²Substance Abuse and Mental Health Services Administration, Office of Applied Studies (2008). *Results from the 2007 National Survey on Drug Use and Health: National Findings* (NSDUH Series H-34, DHHS Publication No. SMA 08-4343). Rockville, MD.

F. Zubsolv is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Zubsolv (buprenorphine and naloxone) sublingual tablets. FDA has determined that Zubsolv (buprenorphine and naloxone) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zubsolv (buprenorphine and naloxone). FDA has determined that Zubsolv (buprenorphine and naloxone) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Zubsolv (buprenorphine and naloxone).

The elements of the REMS include:

- A Medication Guide;
- Elements to assure safe use under 505-1(f)(3)(D) and (E) to ensure that each patient receives Zubsolv sublingual tablets under safe use conditions and is subject to certain monitoring;
- An implementation system to ensure that patients receive Zubsolv sublingual tablets under safe use conditions;
- And a timetable for submission of assessments of the REMS.

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/s/

JUDITH A RACOOSIN
07/03/2013

**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategies (REMS) Review

Date: June 26, 2013

Reviewer(s): Jason Bunting, PharmD
Division of Risk Management

Team Leader: Reema Mehta, PharmD, MPH
Division of Risk Management

Division Director: Claudia Manzo, PharmD
Division of Risk Management

Subject: Review evaluates the Applicant's proposed risk evaluation mitigation strategy (REMS)

Drug Name(s): Zubsolv[®] (buprenorphine/naloxone)

Therapeutic Class: Opioid partial agonist-antagonist

Dosage and Route: 1.4/0.36 mg and 5.7/1.4 mg sublingual tablets

Application Type/Number: NDA 204-242

Applicant/sponsor: Orexo AB

OSE RCM #: 2012-2019

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

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EXECUTIVE SUMMARY

This review documents the Division of Risk Management's final conclusions and recommendations on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Zubsolv (NDA 204-242), originally submitted on September 6, 2012 by Orexo AB. The final proposed REMS for Zubsolv was received on June 21, 2013. The purpose of the REMS is to mitigate the risk of accidental overdose, misuse, and abuse associated with the administration of buprenorphine for maintenance treatment of opioid dependence. The elements of the REMS include a Medication Guide, documentation of safe use conditions, ongoing monitoring requirements, and an implementation system. The timetable for submission of assessments is annually on August 30th, beginning in 2014. The amended REMS for Zubsolv, dated June 21, 2013, contain the appropriate and agreed upon revisions as stipulated by the Agency; therefore, DRISK recommends approval of the REMS.

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review NDA 204-242, Zubsolv[®] (buprenorphine HCl/naloxone HCl dihydrate) sublingual tablets, to assess the need for a risk evaluation and mitigation strategy (REMS) and review the proposed REMS submitted by Orexo AB (Orexo). This review documents DRISK's evaluation of the proposed REMS for Zubsolv.

1.1 BACKGROUND

Zubsolv is a Schedule III, opioid partial agonist-antagonist that is covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). The proposed indication is for the maintenance treatment of opioid dependence to be used as part of a complete treatment program, including counseling and psychosocial support. Zubsolv is available as a sublingual tablet containing 1.4 mg buprenorphine with 0.36 mg naloxone and 5.7 mg buprenorphine with 1.4 mg naloxone. The recommended daily dose for maintenance is 11.4 mg buprenorphine/2.8 mg naloxone given as a single daily dose. Zubsolv is available in unit-dose, child resistant packaging.

Currently, Subutex[®] (buprenorphine HCl) sublingual tablets (NDA 20-732) and Suboxone[®] (buprenorphine HCl/naloxone HCl) sublingual tablets (NDA 20-733) and sublingual film (NDA 22-410), including generics as applicable, are the only approved buprenorphine-containing products for the treatment of opioid addiction in the office-based setting.

Reckitt Benckiser Pharmaceutical's (RBP), Subutex sublingual tablets and Suboxone sublingual tablets were approved by the Agency on October 8, 2002, for the treatment of opioid dependence. These products were approved with Risk Minimization Action Plans (RiskMAPs).

In 2009, the Agency became aware of data showing an increase in misuse and abuse of Subutex and Suboxone, as well as reports of children aged six and younger accidentally exposed to these products. Based on the safety concerns, it was determined by the

Agency that a REMS would be necessary to mitigate the risks of accidental overdose, misuse and abuse.

RBP's, Suboxone sublingual film was approved on August 30, 2010 for use in the maintenance treatment of opioid dependence. As part of the approval of Suboxone sublingual film, the Agency required a REMS to ensure the benefits of the drug outweigh the risks. On December 22, 2011, a similar REMS with the same components was also approved for Subutex sublingual tablets and Suboxone sublingual tablets.

While Subutex and Suboxone are covered under a REMS for their respective products, the applicable generic versions are covered under a comparable, shared REMS, the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS. The BTOD REMS was developed by the Buprenorphine Products Manufacturers Group (BPMG) and contains the same goals and elements as the Subutex and Suboxone REMS programs and was approved along with the applications for several generic versions of these products on February 22, 2013.

The goals of the Subutex, Suboxone, and BTOD REMS are to:

- Mitigate the risks of risks of accidental overdose, misuse, and abuse
- Inform patients of the serious risks associated with [Suboxone]/[Subutex]/[buprenorphine-containing products]

The elements of these REMS include a Medication Guide, elements to assure safe use (ETASU) that include documentation of safe use conditions (ETASU D) and ongoing monitoring requirements (ETASU E), and an implementation system. The timetable for submission of assessments for the Subutex and Suboxone REMS is at 6 months and at 12 months from the date of approval of the REMS, then annually thereafter.

1.2 REGULATORY HISTORY

On July 17, 2012, the Agency advised Orexo to join the other Sponsors in the buprenorphine single shared system REMS during the pre-NDA meeting. Orexo was also advised to submit a REMS that “looks like the approved REMS for Suboxone and Subutex”.

On September 6, 2012, the Agency received Orexo's submission of NDA 204-242 for Zubsolv, which is a 505(b)(2) application with Suboxone as the reference listed drug (RLD). The application was filed on November 5, 2012 and classified as a standard review with a user fee goal date of July 6, 2012. The submission included a proposed REMS that was based on the Suboxone REMS and Orexo indicated in the cover letter for the submission that the Sponsor intended to join the BPMG once it became operational for the development of a single shared system REMS.

On February 7, 2013, the Agency received a background package for a meeting request to discuss proposed enhancements to the Zubsolv REMS program. The proposed enhancements were based on a Failure Mode and Effects Analysis (FMEA) conducted on the current Suboxone REMS program; in which Orexo suggested that they had identified potential failures and gaps, and therefore, developed a more robust REMS for Zubsolv. Additionally, Orexo requested that the enhanced REMS for Zubsolv be implemented independent of the shared BTOD REMS.

A teleconference was held on June 5, 2013 between the Agency and Orexo to discuss the REMS for Zubsolv. During the teleconference, the Agency conveyed to Orexo that based on the information provided in the FMEA, the proposed enhancements to the Zubsolv REMS were not sufficiently supported. Therefore, the REMS for Zubsolv would require the same elements as the BTOD REMS. The Agency again advised Orexo to join the BTOD REMS to minimize burden on stakeholders.

On June 10, 2013, Orexo confirmed their intention to join the BTOD REMS via email and committed to resubmit an amended REMS by June 14, 2013. On June 13, 2013, Orexo communicated via email that it would take 2 weeks to obtain a signed confidentiality agreement from the BPMG in order to obtain access to non-public BTOD REMS documents.

On June 20, 2013, a teleconference was held between the Agency and Orexo to discuss a revised strategy for submission of the Zubsolv REMS due to the inability to become a full member of the BPMG. The Applicant was advised that their REMS would be approved as an interim REMS until Orexo was an active participant of the BPMG; and therefore, is responsible for implementing the REMS as stated in the REMS document until such time. Orexo submitted the final agreed upon Zubsolv REMS documents on June 21, 2013.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Orexo AB's Amended Proposed REMS for Zubsolv (buprenorphine HCl/naloxone HCl dihydrate) sublingual tablet, received June 21, 2013: (eCTD Sequence No. 0016)
- Orexo AB's Amended Proposed REMS for Zubsolv (buprenorphine HCl/naloxone HCl dihydrate) sublingual tablet, received April 8, 2013: (eCTD Sequence No. 0008)
- Orexo AB's Proposed Safe Use Strategy and REMS Enhancement Background Package for Meeting Request, received February 7, 2013: (eCTD Sequence No. 0005)
- Orexo AB's Proposed REMS for Zubsolv (buprenorphine HCL/naloxone HCl dihydrate) sublingual tablet, received September 6, 2012: (eCTD Sequence No. 0000)

3 RESULTS OF REVIEW OF PROPOSED ZUBSOLV RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

The NDA for Zubsolv is a 505(b)(2) application referencing the Agency's previous finding of efficacy and safety for Suboxone sublingual tablets (NDA 20-733). The Applicant's submission indicated that Zubsolv has a higher bioavailability than the RLD; therefore, the Applicant submitted clinical pharmacokinetic data to demonstrate that the 5.7 mg buprenorphine/ 1.4 mg naloxone strength of Zubsolv is bioequivalent to the 8 mg

buprenorphine/2 mg naloxone strength of Suboxone. A biowaiver was requested by the Applicant for the lower 1.4mg buprenorphine/0.36 naloxone strength.

3.2 SAFETY CONCERNS

In 2009, the Agency became aware of data showing an increase in misuse and abuse of Subutex and Suboxone, as well as reports of children accidentally exposed to these products, since their initial approval in October 2002. Reports from postmarketing surveillance revealed an upward trend in indices of extent of abuse of Subutex and Suboxone as noted in interviews of patients entering substance abuse treatment.¹ Additionally, the reports showed that there was illegal trade of buprenorphine products, which involved patients selling, bartering, or giving away their own prescribed medication to friends. The reports also showed that prescribing practices by some physicians contribute to the availability of buprenorphine for abuse and misuse.

Furthermore, Poison Control Center reports reveal an increasing number of cases of accidental exposures to Subutex and Suboxone in children aged six and younger. On a prescription volume-adjusted basis, these Poison Control Center reports involving Subutex and Suboxone are far more common than reports involving other opioid analgesics.

Based on these safety concerns, it has been determined by the Agency that a REMS is necessary to mitigate the risks of accidental overdose, misuse, and abuse. Currently, there are approved REMS for Subutex sublingual tablets, Suboxone sublingual tablets and sublingual film, and the applicable generics of these products covered under the BTOD REMS.

Zubsolv is a buprenorphine-containing product, in which the Agency has determined a REMS is necessary to mitigate the risks of accidental overdose, misuse, and abuse. Overall, the clinical studies supporting approval of the application demonstrated a similar safety profile to that expected for buprenorphine-containing products and did not indicate that there are unexpected adverse events or unusual rates of adverse events associated with Zubsolv.

3.3 APPLICANT'S FINAL PROPOSED REMS FOR ZUBSOLV

3.3.1 Goals

The goals of the Zubsolv REMS are to:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with buprenorphine-containing products

¹ Safety Information included in the REMS Notification letter, dated August 21, 2009.

3.3.2 REMS Elements

3.3.2.1 Medication Guide

A Medication Guide will be dispensed with each prescription for Zubsolv in accordance with 21 CFR 208.24.

The Medication Guide for Zubsolv is part of the Zubsolv REMS and will be available through the Zubsolv REMS website (www.zubsolvrems.com).

3.3.2.2 Elements to Assure Safe Use

3.3.2.2.1 Safe Use Conditions

- a. Zubsolv will only be dispensed by the prescriber or prescribed to patients with documentation of the following safe use conditions:
 - i. Verification that the patient meets the diagnostic criteria for opioid dependence.
 - ii. Risks described in the professional labeling and the Medication Guide have been discussed with the patient.
 - iii. Safe storage of the medication has been explained and reviewed with the patient.
 - iv. After appropriate induction, the patient is prescribed a limited amount of medication at the first visit.
- b. Prescribers will document safe use conditions for each patient by using the 'Appropriate Use Checklist,' or by using another method (e.g. electronic health record) specific to the prescriber's office practice.
- c. Orexo will ensure that within 60 days of FDA approval of the Zubsolv REMS, a Dear Prescriber Letter will be mailed to all prescribers certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This letter is designed to convey and reinforce the risks of accidental overdose, misuse, and abuse of buprenorphine-containing products, as well as the need to appropriately monitor patients and document safe use conditions. The prescriber brochure, *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers*, and the Appropriate Use Checklist will be appended to the Dear Prescriber Letter. The letter will provide instructions on where to obtain copies of the Full Prescribing Information and Medication Guides. Mailings will occur annually thereafter.
- d. Orexo will, on a monthly basis, identify any newly DATA 2000-certified prescribers and mail the applicable documents to them. The prescriber brochure, *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers* and the Appropriate Use Checklist will be appended to the Dear Prescriber Letter. The letter will provide instructions on where to obtain copies of the Full Prescribing Information and Medication Guides.

- e. To further reinforce safe use conditions, Orexo will ensure that within 60 days of FDA approval of the Zubsolv REMS, a Dear Pharmacist Letter will be mailed to all retail pharmacies authorized by DEA to handle schedule III controlled substances on a national mailing list from the National Technical Information Service. The pharmacist brochure, *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists* will be appended to the Dear Pharmacist Letter. The letter will provide instructions on where to obtain copies of the Full Prescribing Information and Medication Guides. Mailings will occur annually thereafter.
- f. Orexo will make the letters and all materials that are appended to the letters available through its toll-free information line, through Zubsolv REMS specialists and on the Zubsolv REMS website.
- g. On a monthly basis, the Zubsolv REMS specialists will make attempts to contact all newly certified prescribers listed on the SAMHSA website and a random sample of existing prescribers via outbound call center calls.
 - 1. The Zubsolv REMS specialists will create awareness of the program, confirm that REMS materials have been received by the prescriber, and confirm understanding of the Zubsolv REMS requirements.
 - 2. The Zubsolv REMS specialists will mail a copy of the REMS materials to prescribers who did not receive or request the REMS materials.
 - 3. The Zubsolv REMS specialists will offer to provide additional follow-up information. If further follow-up is requested, the Zubsolv REMS specialist will offer the following options:
 - Option I: A Zubsolv REMS specialist will provide a live online meeting to review Zubsolv REMS requirements
 - Option II: A Zubsolv REMS specialist will provide a field visit to review Zubsolv REMS requirements

3.3.2.2.2 Monitoring

- a. Each patient using Zubsolv will be subject to the following monitoring:
 - i. Return visits are scheduled at intervals commensurate with patient stability. Weekly, or more frequent, visits are recommended for the first month.
 - ii. Assessment and reinforcement of patient's compliance with the prescribed medication.
 - iii. Assessment of appropriateness of dosage prescribed.
 - iv. Assessment of whether patient is receiving the necessary psychosocial support.
 - v. Assessment of whether patient is making adequate progress towards treatment goals.

- b. Prescribers will document that each patient has received the required clinical monitoring using the ‘Appropriate Use Checklist,’ or by using another method/system (e.g. electronic health record) specific to the prescriber’s office practice.

The following materials are part of the Zubsolv REMS and are appended to the REMS document:

- Dear Prescriber Letter
- Dear Pharmacist Letter
- Appropriate Use Checklist
- Prescriber Brochure, “*Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers*”
- Pharmacist Brochure, “*Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*”
- Zubsolv REMS Website (www.zubsolvrems.com)

3.3.2.3 Implementation System

Orexo will:

- Ensure that all DATA 2000-certified prescribers receive the Dear Prescriber Letter with the appended materials.
- Monitor compliance with the prescriber requirements to document prescribing and dispensing with documentation of safe use conditions through surveys of patients and prescribers, evaluations of health care utilization databases, and ongoing surveillance (sources including, but not limited to, internet, national databases, and surveys conducted at substance abuse treatment programs).
- Monitor and evaluate the implementation of the elements to assure safe use provided for under Sections B1, above, and in the manner described in the REMS supporting document, and take reasonable steps to improve implementation of these elements to meet the goals of the Zubsolv REMS, if the goals of the REMS are not being met.

3.3.2.4 Timetable for Submission of Assessments

REMS assessments will be submitted to the FDA at each year, on August 30th, beginning in 2014. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. The NDA holder(s) will submit each assessment so that it will be received by the FDA on or before the due date.

3.3.3 REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the approval letter. The information needed for assessment will include at a minimum:

1. An evaluation of patients' awareness and understanding of the serious risks associated with buprenorphine-containing products
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
4. An evaluation of prescribers' awareness and understanding of the serious risks associated with buprenorphine-containing products
5. An evaluation of pharmacists' awareness and understanding of the serious risks associated with buprenorphine-containing products
6. An analysis to evaluate utilization patterns of buprenorphine-containing products including frequency of office visits, amount dispensed in prescriptions to new patients, and other indicators of adherence to practices important to safe use.
7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from signals of abuse, misuse, overdose and addiction. Surveillance will include, among other sources, reports of pediatric exposures
8. Monitoring and evaluation of the implementation of the ETASU
9. An assessment of the extent to which the REMS is meeting its goals. Specific measures that will be proposed to increase awareness if surveys of patients, prescribers, and pharmacists indicate that awareness is not adequate.

4 DISCUSSION

A REMS for Zubsolv is required to ensure the benefits of the drug outweigh the risks of accidental overdose, misuse, and abuse. During review of the application, the Applicant proposed a REMS with enhancements based on a FMEA utilizing the currently approved REMS for Suboxone.

DRISK and the Division of Medical Error Prevention and Analysis (DMEPA) evaluated the FMEA and determined that it was incomplete and lacked critical information to perform a full evaluation of the FMEA. Based on this evaluation of the FMEA, DRISK determined that the Subutex, Suboxone, and BTOD REMS programs in their current form are sufficient to mitigate the risks associated with these products and no enhancements as proposed by the Applicant were warranted. Furthermore, the clinical studies supporting approval of the application demonstrated a similar safety profile to that expected for buprenorphine-containing products and did not indicate that there are unexpected adverse events or unusual rates of adverse events associated with Zubsolv.

After consultation with senior management, DRISK and DAAAP informed the Applicant that based on the information provided in the FMEA, the proposed enhancements are not sufficiently supported. Therefore, the REMS for Zubsolv would require the same elements as the BTOD REMS. DRISK advised Orexo to join the BTOD REMS to minimize burden on stakeholders. Orexo agreed to join the BTOD REMS however, due to the legal agreements that must take place between members of the BPMG, becoming a full active member prior to the action date of July 6, 2013 would not be possible. Therefore, Orexo was informed that an interim REMS for Zubsolv would be approved for the application while Orexo worked with the BPMG to become a full active member for the BTOD REMS.

The interim REMS for Zubsolv contains goals and elements comparable to that of the BTOD REMS with Orexo company specific and Zubsolv product specific information included. Orexo agreed to this strategy and on June 21, 2013, resubmitted the final interim REMS documents that were previously agreed upon via teleconference on June 20, 2013. In their June 21, 2013 submission, Orexo stated in their cover letter that this REMS would serve on an interim basis until Zubsolv is successfully included in the BPMG and that Orexo will continue to work with the BPMG to become a member of the BTOD REMS.

5 CONCLUSION

In conclusion, the amended REMS for Zubsolv (buprenorphine HCl/naloxone HCl dihydrate), sublingual tablets containing 1.4 mg buprenorphine with 0.36 mg naloxone and 5.7 mg buprenorphine with 1.4 mg naloxone, submitted June 21, 2013 contains the appropriate and agreed upon revisions on the REMS documents and materials as stipulated by the Agency on June 20, 2013. The REMS Supporting Document outlines the information and content that the Applicant will use to assess the effectiveness of the Zubsolv REMS in achieving the goals.

Therefore, the Zubsolv REMS is compliant under FDAAA and acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the Zubsolv REMS, as appended to this review, to serve as an interim REMS while the Applicant becomes a full active member of the BPMG and integrates Zubsolv into the BTOD REMS.

In addition, we recommend that the following language be included in the approval letter:

We refer to your email communication dated June 7, 2013, expressing your agreement to join the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) shared REMS program and indicating that communication with the Buprenorphine Products Manufacturing Group (BPMG) has been initiated. The Zubsolv REMS will serve as an interim REMS until the time you become a full active member of the BPMG. You will then be required to submit a modified REMS through the BPMG incorporating Zubsolv into the shared system.

The Zubsolv REMS Assessment Plan (Section 3.4 REMS Assessment Plan) must also be included in the REMS Approval Letter (REMS Section).

ATTACHMENTS

Zubsolv REMS Document

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/s/

JASON A BUNTING
06/27/2013

CLAUDIA B MANZO
06/27/2013
concur

NDA 204242

**ZUBSOLV® (buprenorphine hydrochloride and naloxone hydrochloride
dihydrate) sublingual tablets CIII**

Opioid Partial Agonist-Antagonist

Orexo US, Inc.
220 E. 42nd Street, Ste. 409A
New York, NY 10017, USA
Telephone: (855) 673-9687

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

This REMS applies to Zubsolv indicated for the maintenance treatment of opioid dependence. This REMS does not apply to Zubsolv that is dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SUPPORTING DOCUMENT**

Confidential

This document is a confidential communication of Orexo AB. All information and data contained within this document are confidential and trade secret. No information contained herein may be divulged or disclosed to third parties without prior written approval from Orexo AB.

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1. BACKGROUND

1.1 Introduction

This Risk Evaluation and Mitigation Strategy (REMS) is designed to mitigate the risks of accidental overdose, misuse, and abuse with the use of Zubsolv[®] (buprenorphine hydrochloride and naloxone hydrochloride dihydrate) sublingual tablets CIII (Zubsolv) and to inform patients of the serious risks associated with buprenorphine /naloxone sublingual tablets used to treat patients who are opioid-dependent.

This REMS does not apply to buprenorphine/naloxone sublingual tablets dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

1.2 Current Situation

Pursuant to 505-1(f)(1), FDA has determined that buprenorphine HCl and naloxone sublingual tablet can be approved only if elements necessary to assure safe use are required as part of a Risk Evaluation and Mitigation Strategy (REMS). Through FDA guidance and recommendation, Orexo has contacted the Buprenorphine Product Management Group (BPMG) to gain acceptance and coordinate the current Zubsolv REMS to be a part of the FDA approved Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS.

The Zubsolv REMS is designed to (1) mitigate the risks of accidental overdose, misuse, and abuse and (2) to ensure prescribers, pharmacists, and patients are appropriately informed of the serious risks associated with the use of Zubsolv. The elements to assure safe use will inform prescribers, pharmacists, and patients of the serious risks associated with Zubsolv and the appropriate conditions of safe use and storage of Zubsolv. The elements to assure safe use will also ensure adequate clinical monitoring of patients by the healthcare providers.

Buprenorphine/naloxone is a product approved for the treatment of opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). DATA 2000 allows qualifying physicians to apply for a waiver to distribute and prescribe Schedule III, IV, and V narcotics to patients in the office setting for the treatment of opioid addiction. Stipulations of DATA 2000 include the assignment of a special DEA identification number for qualifying physicians, as well as limitations imposed on the number of patients a single physician can treat concurrently².

1.3 Product Description

Zubsolv is supplied as 1.4-mg buprenorphine/0.36-mg naloxone and 5.7-mg buprenorphine/1.4-mg naloxone rapidly disintegrating (b) (4)-flavored sublingual tablets. The tablets are white and dosage strengths are differentiated by shape and debossing on one side of the tablet. The lower strength is an arc triangle (base 7.2 mm, height 6.9 mm) flat-faced,

radius-edged tablet debossed with 1.4, representing 1.4 mg buprenorphine. The higher strength is a round flat-faced radius-edged tablet 7 mm in diameter debossed with 5.7, representing 5.7 mg buprenorphine. Zubsolv is packed in individually sealed ten count aluminum/aluminum child resistant (F=1) blister cards. (b) (4)

. The final commercial product in blister cards will be packed in a cardboard carton. Each carton will contain 3 ten count blister cards, in total 30 tablets. One Medication Guide will be enclosed within each carton along with the Full Prescribing Information at the time of final product assembly

Due to a higher bioavailability of the Zubsolv formulation, tablet strengths are reduced compared to other buprenorphine products in order to give equivalent systemic buprenorphine exposure (as shown in table below).

Corresponding doses of buprenorphine products that contain naloxone		
Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual film	Zubsolv sublingual tablets
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone

Addressing education needs associated with these doses resonates well with the over-arching need to encourage appropriate prescribing and dispensing practices, striving for each patient to receive only the lowest effective dose required to curtail opioid withdrawal symptoms.

Buprenorphine is classified as a Schedule III narcotic by the FDA under the Controlled Substances Act (CSA) based on its low bioavailability and limited maximal opioid effects, which are less than those of Schedule II narcotic products, such as morphine and levo-alpha acetyl methadol (LAAM)¹. The US Drug Enforcement Agency (DEA) has imposed specific regulations regarding the storage, distribution, accountability, prescribing practices, and usage of controlled substances, such as buprenorphine, as stated in 21 CFR 1301.

1.4 Risks Associated with Zubsolv Sublingual Tablets

1.4.1 Overdose, Misuse, and Abuse

As with all opioid products, there is the potential for overdose, misuse, and abuse of the Zubsolv medication. The misuse and abuse of buprenorphine can lead to serious health consequences, including respiratory depression and death, when used concurrently with central nervous system (CNS) depressants, such as benzodiazepines, other opioids, or alcohol^{3,6}. The most common form of buprenorphine abuse involves crushing the sublingual tablets and injecting their extractions intravenously.

Analysis on diversion of buprenorphine/naloxone and buprenorphine-only products highlights the absence of specific clinical and counseling efforts towards minimizing overprescribing of these products. The practice of diverting buprenorphine containing products is well described for opioid-addicted patients, in part as a means to fund out-of-pocket expenses to obtain the next prescription⁵. Patients may obtain a quantity greater than their therapeutic needs through visiting one or multiple doctors and either use the excess amount for personal use, or divert them to illegal markets. Other possible methods of diversion include theft from pharmacies and physician offices, as well as illegal importation into the country. Formulations of buprenorphine approved only for use in countries outside the US have shown up in US monitoring systems, indicating that illegal importation of these products into the US is occurring on some level³. Diversion of buprenorphine/naloxone can occur but is lower than for other opioids perhaps because the combination therapy precipitates withdrawal symptoms when taken concurrently with high-dose opioids³.

1.5 Benefits Associated with Zubsolv

Buprenorphine in this combination formulation is currently available under DATA 2000 used to treat patients with opioid addiction in a physician office setting. Easier access to this treatment option has the potential to benefit many more individuals who are addicted to opioids who otherwise may have gone without treatment.

Historically, the only option for the treatment of opioid abuse has been at a clinic or facility that specialized in addiction treatment. In some cases, this required the patient to travel long distances, making treatment inaccessible or impossible for some. With the approval of buprenorphine/naloxone, treatment of opioid abuse has become available to a wider patient base^{3,4,7}.

Buprenorphine has a more favorable safety profile over full agonist opioids, such as heroin or methadone, as it may produce a lesser degree of sedation and respiratory depression in users. The combination of buprenorphine and naloxone also reduces cravings and withdrawal symptoms from other opioid products without any significant impairment to cognitive or motor functions⁴.

2. GOALS

The goals of the Zubsolv REMS are to:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with buprenorphine-containing products

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prescribers, and pharmacists indicate that awareness is not adequate.	
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5. OTHER RELEVANT INFORMATION

Not applicable

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