

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204242Orig1s000**

**REMS**

**Initial REMS approval: 07/2013**

**NDA 204242**

**ZUBSOLV<sup>®</sup> (buprenorphine hydrochloride and naloxone hydrochloride dihydrate) sublingual tablets CIII**

Opioid Partial Agonist-Antagonist

Orexo US, Inc.  
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New York, NY 10017, USA  
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**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.*

**I. 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

**II. REMS ELEMENTS:**

**A. 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](http://www.zubsolvrems.com)).

## **B. Elements to Assure Safe Use**

### **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

## 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](http://www.zubsolvrems.com))

### **C. 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.

### **D. Timetable for Submission of Assessments**

REMS assessments will be submitted to the FDA at each year, on August 30<sup>th</sup>, 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.

## IMPORTANT DRUG WARNING

**Subject: Risk Evaluation and Mitigation Strategy (REMS) for Zubsolv® for opioid dependence due to the risks of accidental overdose, misuse, and abuse.**

Dear Prescriber:

You are receiving this letter because you are a prescriber certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000).

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) for Zubsolv. This REMS does not apply to Zubsolv that is dispensed to patients in an Opioid Treatment Program (OTP) under 42 CFR Part 8.

The FDA has determined that a REMS is necessary to ensure that the benefits of Zubsolv for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Zubsolv is indicated for the maintenance treatment of opioid dependence and is used as part of a complete treatment plan, including counseling and psychosocial support.

### **Serious Risks of Zubsolv**

The following key messages need to be communicated to patients about the risks of accidental overdose, misuse, and abuse while taking Zubsolv:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) while taking Zubsolv. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.
- Instruct patients to keep Zubsolv in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed to Zubsolv, medical attention should be sought immediately.
- Advise patients that Zubsolv contains an opioid that can be a target for people who abuse prescription medications or street drugs. Caution patients to keep their Zubsolv in a safe place, and to protect them from theft.
- Instruct patients never to give Zubsolv to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away Zubsolv is against the law.

### **Prescriber Action**

Certified prescribers must read the enclosed educational brochure entitled ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers***. Under the Zubsolv REMS program, prescribers are strongly encouraged to perform and document all of the following actions:

- Verify the patient meets diagnostic criteria for opioid dependence
- Discuss the risks associated with Zubsolv, including those described in the Medication Guide
- Provide induction doses under appropriate supervision
- Prescribe a limited amount of medication to the patient that will last until the next visit
- Explain how to safely store the medication out of reach of children
- Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month)
- Consider “pill count”/dose reconciliation
- Assess whether the patient is receiving the counseling/psychosocial support considered necessary for treatment
- Assess whether the patient is making progress toward treatment goals, including, as appropriate, urine toxicology testing
- Continually assess appropriateness of maintenance dose
- Continually assess benefits of treatment outweigh the risks

### **Patient Monitoring and Appropriate Dosing Info**

An *Appropriate Use Checklist* is enclosed to assist you in performing and documenting the above prescriber actions of the Zubsolv REMS. You may use the enclosed checklist or other means (e.g. electronic health record) specific to your office practice to document that the above actions have been completed for each patient.

### **Medication Guide**

The Zubsolv REMS includes a Medication Guide with important information to be reviewed with patients. In addition, the Medication Guide will be dispensed with each prescription for Zubsolv.

### **Reporting Adverse Events**

To report SUSPECTED ADVERSE EVENTS contact:

- Orexo US, Inc. by phone at 1-888-ZUBSOLV (1-888-982-7658) or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This letter is not a comprehensive description of the risks associated with the use of Zubsolv. Additional important safety information can be found in the *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers* educational brochure and Full Prescribing Information.

Additional copies of the educational brochure, *Appropriate Use Checklist*, Full Prescribing Information, and Medication Guide for Zubsolv, can be obtained at [www.zubsolvrems.com](http://www.zubsolvrems.com) or by contacting the toll-free call center at 1-877-ZUBSOLV (1-877-982-7658).

Sincerely,

Peter Hjelmström, MD, PhD, Assoc Prof  
Chief Medical Officer  
Head of Clinical Development

*Enclosures: Appropriate Use Checklist*

*Office-Based Buprenorphine Therapy for Opioid Dependence: Important  
Information for Prescribers*

# Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers

Zubsolv<sup>®</sup>

## I. Introduction

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) to prescribers of Zubsolv, a buprenorphine-containing product combined with naloxone, who are certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). 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 (OTP) under 42 CFR Part 8.

This brochure summarizes important safety issues and messages needed to manage and counsel patients about safe use of Zubsolv.

### **What are buprenorphine-containing products?**

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with naloxone.

Buprenorphine-containing products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction.

Some buprenorphine-containing products include a second active ingredient, naloxone HCl, intended to deter individuals from abusing buprenorphine-containing products by the intravenous route. Products containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence.

Buprenorphine-containing products are used as part of a complete treatment plan, including counseling and psychosocial support.

### **What are the primary differences among the buprenorphine products that contain naloxone?**

The primary differences are the available dosage strengths, recommended doses, and formulations. The available dosage strengths and recommended doses vary based on the bioavailability for each product (i.e., how much of the buprenorphine is absorbed after administration). Suboxone<sup>1</sup> sublingual tablets, including generic equivalents, are available as 2 mg buprenorphine/0.5 mg naloxone and 8 mg buprenorphine/2 mg naloxone dosage strengths. Zubsolv sublingual tablets are available as 1.4 mg buprenorphine/0.36 mg naloxone and 5.7 mg buprenorphine/1.4 mg naloxone dosage strengths. Buprenorphine/naloxone sublingual film is available as 2 mg buprenorphine/0.5 mg naloxone, 4 mg buprenorphine/1 mg naloxone, 8 mg buprenorphine/2 mg naloxone, and 12 mg buprenorphine/3 mg naloxone dosage strengths.

Patients being switched between different formulations should be started on the corresponding dose (as shown in the table below) compared to the previously administered product. Patients

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<sup>1</sup> Buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone<sup>®</sup> are covered under the Suboxone REMS program.

should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated<sup>2</sup>.

<b>Corresponding doses of buprenorphine products that contain naloxone</b>		
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

## **II. REMS – Risk Evaluation and Mitigation Strategy**

### **What is a Risk Evaluation and Mitigation Strategy (REMS)?**

A REMS is a strategy to manage a known or potential risk associated with a drug. A REMS can include, among other strategies, a Medication Guide, a communication plan, and elements to assure safe use.

### **Is there a REMS for Zubsolv?**

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with Zubsolv outweigh the potential risks.

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 the use of buprenorphine-containing products

### **What is my role with regard to the Zubsolv REMS?**

To meet the requirements of the REMS and to ensure the benefits of prescribing Zubsolv outweigh the risks of accidental overdose, misuse, and abuse. Prescribers should take the following measures and document actions taken with each patient to ensure safe use conditions:

- Verify the patient meets diagnostic criteria for opioid dependence

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<sup>2</sup> Note that, although the nominal Suboxone sublingual film doses are the same as the Suboxone sublingual tablets and generic equivalent tablets, not all strengths and combinations of the films are bioequivalent to the tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

- Discuss the risks associated with Zubsolv, including those described in the Medication Guide
- Provide induction doses under appropriate supervision
- Prescribe a limited amount of medication to the patient that will last until the next visit
- Explain how to safely store the medication out of reach of children
- Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month)
- Consider “pill count”/dose reconciliation
- Assess whether patient is receiving counseling/psychosocial support considered necessary for treatment
- Assess whether patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing)
- Continually assess appropriateness of maintenance dose
- Continually assess whether or not benefits of treatment outweigh the risks

As part of the Zubsolv REMS, prescribers of Zubsolv should document safe use conditions and 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. This can be retained in the records of each patient. Additional copies of the *Appropriate Use Checklist* can be obtained online at [www.zubsolvrems.com](http://www.zubsolvrems.com) or by calling 1-877-ZUBSOLV (1-877-982-7658).

### **III. Highlighted Important Safety Information for Buprenorphine-Containing Products**

This section of the brochure highlights important safety information to consider when prescribing buprenorphine-containing products, including Zubsolv. **Refer to the Full Prescribing Information (FPI) for detailed safety-related information for Zubsolv.**

#### ***Abuse Potential for Buprenorphine-Containing Products***

##### **Are buprenorphine-containing products abusable?**

Yes, buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse, misuse, or diversion of this product.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant use of buprenorphine and alcohol and other substances, especially benzodiazepines.

The prescriber may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal request of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication by the patient are appropriate measures that help to limit abuse of opioid drugs.

Due to the partial agonist properties of buprenorphine, buprenorphine-containing products may precipitate opioid withdrawal signs and symptoms in persons dependent on full opioid agonists if administered before the agonist effects of the opioid have subsided. However, buprenorphine products that contain naloxone are highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Therefore, to discourage misuse or abuse, it is highly recommended that, for unsupervised administration, buprenorphine with naloxone rather than buprenorphine alone is prescribed whenever feasible after induction.

However, clinicians should also be aware that some opioid-dependent persons can and do abuse buprenorphine/naloxone combinations by the intravenous or intranasal route, in particular opioid-dependent persons with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

### **Can buprenorphine-containing products cause dependence?**

Yes, buprenorphine is a partial agonist at the mu-opioid receptor. Chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. If cessation of therapy is indicated, it is appropriate to taper the buprenorphine dose, rather than abruptly discontinue the medication. Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing buprenorphine in situations where there is an increased concern about the possibility of misuse, diversion, or abuse.

### **What precautions should I take in my practice to prevent diversion and abuse?**

You should consider the following suggestions:

- Initiate treatment with supervised administration, progressing to unsupervised administration as your patient's clinical stability permits
- Limit the use of buprenorphine-only products, such as buprenorphine sublingual tablets, to supervised use, wherever possible. Point out to the patient that some buprenorphine-containing products also contain naloxone. The naloxone is likely to precipitate withdrawal signs and symptoms when injected by individuals dependent on heroin, morphine, or other full opiate agonists. It is strongly recommended that buprenorphine/naloxone products be used whenever unsupervised administration is planned

- As your patients progress beyond induction to a stabilized dose, consider a longer-term prescription of buprenorphine-containing product to be taken at home. When determining the quantity of buprenorphine-containing product to be prescribed, you should consider your patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of medication in an unsupervised environment
- Have plans in place to deal with patient requests for replacement of prescriptions or supplies of medication that are described as lost or stolen
- Keep tight control of your prescription pads. Never leave them in the examination room, even inside a desk drawer. Never sign an incomplete prescription blank
- Write all numbers (quantity and strength) in both numbers and letters - like you would write a personal check
- Establish a relationship with the pharmacies you expect to be filling your prescriptions. Discuss potential diversion problems and controls with them
- Maintain copies of photo (or other) I.D. and Social Security numbers in patients' records
- If you suspect an attempt to divert prescription medications, unsupervised administration privileges should be reevaluated. Carefully consider options such as random drug testing or a callback to verify adherence to program rules. In a callback, the patient receives an unannounced phone call and must show up at the prescriber's office within a reasonable period (e.g., 24 to 36 hours) with all prescribed medications. In this case, the amount of medication remaining must correspond to the amount expected based on prescribed dosing. If this program is implemented, prescribers should clearly state their policy to patients in advance.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids, despite implementation of the above precautions, should be provided or referred for more intensive and structured treatment.

### **How can patients prevent accidental exposure to buprenorphine-containing products in children?**

Patients should be instructed to keep buprenorphine-containing products in a secure place, out of the sight and reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed accidentally to a buprenorphine-containing product, seek immediate urgent medical attention.

### **What is an appropriate medical response to overdose on buprenorphine-containing product?**

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone hydrochloride may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

## ***Contraindications***

- Hypersensitivity to buprenorphine and, in the case of combination products, naloxone

## ***Warnings and Precautions***

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol)
- Consider dose reduction of CNS depressants, buprenorphine-containing products, or both in situations of concomitant prescription
- Store buprenorphine-containing products safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events
- Do not administer buprenorphine-containing products to patients with known hypersensitivity to buprenorphine or, in the case of combination products, naloxone
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of buprenorphine-containing products by individuals physically dependent on full opioid agonists before the agonist effects of other opioids have subsided, particularly buprenorphine-containing products that also contain naloxone.
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- Buprenorphine-containing products indicated for the treatment of opioid dependence are not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose
- Caution patients about the risk of driving or operating hazardous machinery

## ***Adverse Reactions***

- Adverse events most commonly observed with buprenorphine-containing products are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. For a complete list of potential adverse events associated with buprenorphine-containing products, please see the Full Prescribing Information.
- To report SUSPECTED ADVERSE REACTIONS, contact
  - The manufacturer of the product taken or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

### ***Drug Interactions***

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing
- Use caution in prescribing buprenorphine-containing products for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse

### ***Use in Specific Populations***

- Buprenorphine-containing products are not indicated for use during pregnancy unless potential benefit justifies potential risk
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking buprenorphine-containing products
- Safety and effectiveness of buprenorphine-containing products in patients below the age of 16 have not been established
- Administer these products with caution to elderly or debilitated patients
- Administer buprenorphine-containing products with caution in patients with liver dysfunction

## **IV. Prescribing Buprenorphine-Containing Products**

### **When should products containing buprenorphine with naloxone be prescribed?**

Buprenorphine products that include naloxone are indicated for maintenance treatment of opioid dependence and are preferred over buprenorphine-only products for unsupervised administration.

### **What is the proper protocol for induction?**

Products containing buprenorphine alone are preferred for use during induction. Prior to induction, consideration should be given to the type of opioid dependence, the time since last opioid use, and the degree or level of opioid dependence (see package insert for complete instructions).

To avoid inadvertently precipitating opioid withdrawal, induction should be undertaken when clear and obvious signs of withdrawal are evident. A clinical tool to assess withdrawal should be used. For example, the Clinical Opioid Withdrawal Scale (COWS) can be used and a score of >12 should be recorded on the COWS before the first dose is administered.

In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period. Therefore, it is recommended that an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal signs and symptoms.

### **How should I schedule office visits: how much involvement should I have?**

During the induction period, it is recommended that the initial dose(s) be provided under supervision and that no more than 1 to 2 days of products containing buprenorphine alone for take-home use be provided on each of the 2 to 3 visits during the first week of treatment.

Patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Products containing buprenorphine with naloxone should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient assessment.

Once a stable dosage has been achieved and toxicological tests do not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of products containing buprenorphine with naloxone who are making progress toward the treatment objectives. Continuation or modification of pharmacotherapy should be based on the prescriber's evaluation of treatment outcomes and objectives such as:

1. Absence of buprenorphine toxicity
2. Absence of medical or behavioral adverse effects
3. Responsible handling of buprenorphine-containing product by the patient
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use)

If treatment goals are not being achieved, the prescriber should reevaluate the appropriateness of continued treatment. Patients who continue to misuse, abuse or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

### **How do I manage in-office induction doses without maintaining a supply in my office?**

For those prescribers who do not wish to maintain a supply of buprenorphine-containing products in their offices, it is important to develop a good working relationship with your local pharmacies. To ensure that you will be able to exchange information with the pharmacist, such as confirming the validity of your induction prescriptions, it is recommended that you have the patient sign a release of information at the time of the initial office visit. A sample consent form with all the elements required under 42 CFR Part 2.31 is included in Appendix A of this brochure.

On the day of induction, write a prescription **only** for the induction day's dosage. Instruct your patient (or, if available, a trustworthy family member accompanying the patient) to take the prescription to the pharmacy, have it filled and bring it back to your office for dosing.

It is recommended that you call or fax ahead to the pharmacy to ensure availability of the medication and to reduce patient waiting time. You should instruct the patient not to take the dose until he or she returns to the office. The induction dose will be administered, and he or she will be monitored, in your office. The pharmacist should reiterate this instruction upon filling the prescription.

Note that it is illegal for prescribers to hold medication in the office that is prescribed for a specific patient. Therefore, you should limit the prescription to one day's dose, and repeat this method for the first several days of treatment before providing a prescription for several days' supply at one time.

### **Will prescriptions be valid at any pharmacy, or will I need to refer patients to a specific location?**

Prescriptions specifying a buprenorphine-containing product will be valid at any pharmacy authorized by DEA to handle schedule III controlled substances. However, prior to prescribing buprenorphine-containing products it is essential that you establish a relationship with one or more specific pharmacies in your area that will be in a position to provide your patients with initial doses, as well as instructions for returning to your office for induction and the follow-up prescription.

Generally, a pharmacy near your office is recommended for patient convenience.

### **What storage and record-keeping requirements are associated with treating patients for opioid dependence with buprenorphine-containing products?**

If you wish to maintain a supply of buprenorphine-containing products in your office for the purpose of dispensing to patients during induction, you will be required to keep the medications in a secure environment. According to federal requirement, they must be kept in a securely locked, substantially constructed cabinet. You will also be required to maintain a written record of the disposition of all doses. Usually this can be done with the maintenance of a logbook in which you record all incoming doses and account for each dispensed dose as it is used. This record must be kept current at all times. Additional requirements may be in place in your state. You are also required to take an inventory every 2 years, and to keep records of all receipts.

In addition, prescribers of buprenorphine-containing products should keep accurate and complete records for each patient that include:

1. The medical history and physical examination
2. Diagnostic, therapeutic, and laboratory results
3. Evaluations and consultations
4. Treatment objectives
5. Discussion of risks and benefits
6. All treatments that the patient is receiving
7. Medications (including date, type, dosage, and quantity prescribed and/or dispensed to each patient)

8. A physical inventory of all Schedule III, IV, and V controlled substances on hand that are dispensed by the prescriber in the course of maintenance or detoxification treatment of an individual
9. Instructions and agreements
10. Periodic reviews

Records should remain current and be maintained in an accessible manner and readily available for review. Prescribers must adhere to the special confidentiality requirements of 42 CFR Part 2.

### **Are there special confidentiality issues I should consider?**

Remember that you may be communicating with the pharmacist to verify prescriptions for a particular patient. There are special federal regulations concerning the confidentiality of substance abuse treatment records (42 CFR Part 2), and the privacy of health records (Health Insurance Portability and Accountability Act [HIPAA]). To ensure that you will be able to exchange information with the pharmacist, such as confirming the validity of a prescription for a buprenorphine-containing product, it is recommended that you have the patient sign a release of information at the time of the initial office visit. A sample consent form with all the elements required under 42 CFR Part 2.31 is included in Appendix A of this brochure. It is particularly important to obtain the patient's consent if you elect to phone or fax in prescriptions, as this constitutes disclosure of the patient's treatment. When the prescription is directly transmitted by the prescriber, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42 CFR Part 2.31 does not apply when it is the patient who delivers the prescription to the pharmacist, without direct communication from the prescriber to the pharmacist.

To learn more about these regulations, visit the SAMHSA website, <http://buprenorphine.samhsa.gov>, or call 1-866-BUP-CSAT (1-866-287-2728).

## ***Dosing and Administration of Buprenorphine-containing Products***

### **How do I maintain clinically effective dosing for stabilized patients?**

The recommended target dose is 16 mg buprenorphine/4mg naloxone per day for Suboxone sublingual tablets and sublingual film, including generic equivalents, and is 11.4 mg buprenorphine/2.8 mg naloxone per day for Zubsolv sublingual tablet. Clinical studies have shown that these are clinically effective doses. Although lower doses may be effective in some patients, for most patients, this dose should alleviate withdrawal symptoms and block or attenuate the effects of other opioid agonists for at least 24 hours.

The upper limit of the recommended dose is 24 mg per day for Suboxone sublingual tablets and sublingual film, including generic equivalents, and 17.1 mg per day for Zubsolv. The reported lack of significant increase in brain mu-receptor occupancy between the target dose and twice the target dose implies that there should be little difference in clinical effectiveness at doses between the target dose and the recommended upper limit daily dose. When a patient expresses a need for a higher dose, consider the possible causes (e.g., environmental stressors or psychosocial issues that increase cravings or possible drug interactions). Before increasing the patient's dose,

explore other alternatives. Also consider the possibility that the patient may be exaggerating symptoms to obtain additional medication for diversion.

### **How should buprenorphine-containing products be administered?**

Tablets should be placed under the tongue until they are dissolved. For doses requiring the use of more than 2 tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than 2 tablets comfortably), place 2 tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

### **How should I manage patients who are not compliant with therapy?**

Prescribers will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention, such that the prescriber does not feel that he or she has the expertise to manage the patient. In such cases, the prescriber may want to assess whether to refer the patient to a specialist and/or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

## ***Discontinuing Therapy with Buprenorphine-Containing Products***

### **What can I tell patients who wish to discontinue treatment?**

Patients should be advised not to change the dose of buprenorphine-containing products without consulting their prescriber. Patients seeking to discontinue treatment with buprenorphine-containing products for opioid dependence should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist medication-assisted treatment.

If a dependent patient abruptly discontinues use of these products, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the dose of these products, rather than abruptly discontinue it. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

## **V. Psychosocial Support and Other Patient Counseling**

### **How important is counseling for my patients and my practice?**

Pharmacotherapy is only one aspect of treatment. Psychosocial counseling is an essential component of treatment for opioid dependence. Because it is such a crucial element, DATA 2000 requires that prescribers seeking to obtain the certification to prescribe buprenorphine-containing products must be able to provide or refer patients for counseling.

In addition to services typically provided by prescribers, counseling may incorporate such elements as motivational enhancement therapy, cognitive behavioral therapy, prevention education, and intervention in case of relapse.

If counseling is provided by an individual other than the prescriber, it is essential that the counselor partner with the prescriber in providing care. The counselor can provide an additional measure of monitoring for adherence and treatment response.

### **What safety conditions need to be communicated to patients about buprenorphine-containing products?**

Review the contents of the Medication Guide, in its entirety, with each patient, including the following:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking any buprenorphine-containing product. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their prescriber.
- Instruct patients to keep buprenorphine-containing products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed to one of these products, medical attention should be sought immediately.
- Advise patients that buprenorphine-containing products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their products in a safe place, and to protect them from theft.
- Instruct patients never to give buprenorphine-containing products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away buprenorphine-containing products is against the law.
- Caution patients that buprenorphine-containing products may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken especially during induction and dose adjustments and until patients are reasonably certain that therapy with a buprenorphine-containing product does not adversely affect their ability to engage in such activities.
- Advise patients not to change the dose of the buprenorphine-containing product without consulting their prescriber.
- Advise patients to take the buprenorphine-containing product once a day as directed.
- Inform patients that the buprenorphine-containing products can cause drug dependence of the opioid type. Withdrawal signs and symptoms may occur when the medication is discontinued.
- Advise patients seeking to discontinue treatment with the buprenorphine-containing product for opioid dependence to work closely with their prescriber on a tapering schedule and apprise them of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Caution patients that, like other opioids, buprenorphine-containing products may produce orthostatic hypotension in ambulatory individuals.

- Ask patients if other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used.
- Advise patients who become pregnant, or are planning to become pregnant, to consult their prescriber regarding the possible effects of using buprenorphine-containing products during pregnancy.
- Warn patients that buprenorphine passes into breast milk and breast-feeding is therefore not advised in mothers treated with buprenorphine-containing products.
- Ask patients to inform their family members or other appropriate individuals that, in the event of emergency, the treating prescriber or emergency department staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with a buprenorphine-containing product
- Instruct patients to dispose of unused buprenorphine-containing product as soon as it is no longer needed. Unused tablets should be flushed down the toilet.

## **VI. Where Can I Get More Information on Treating Patients with Buprenorphine-Containing Products?**

Refer to the package insert for Full Prescribing Information, which can be found at [www.zubsolvrems.com](http://www.zubsolvrems.com).

Additional recommendations may be found in treatment guidelines available free from the Center for Substance Abuse Treatment (CSAT) at the Substance Abuse and Mental Health Services Administration. Additional information is also available on the CSAT Buprenorphine Information Center website at <http://buprenorphine.samhsa.gov>.

General information about buprenorphine treatment and treatment of addiction are available through numerous sources including, but not limited to:

- American Society of Addiction Medicine website ([www.asam.org](http://www.asam.org))
- American Academy of Addiction Psychiatry website ([www.aaap.org](http://www.aaap.org))
- Physician Clinical Support System - Buprenorphine (<http://pcssb.org>)

# Appendix A

## Sample 42 CFR Part 2.31 Consent Form

1. I (name of patient) \_\_\_\_\_
2. Authorize Dr. \_\_\_\_\_
3. To disclose any information needed to confirm the validity of my prescription and for submission for payment for the prescription.
4. To the dispensing pharmacy to whom I present my prescription or to whom my prescription is called/sent/faxed, as well as to third party payors.
5. For the purpose of assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.
6. Date (on which this consent is signed)  
\_\_\_\_\_
7. Signature of patient  
\_\_\_\_\_
8. Signature of parent or guardian (where required)  
\_\_\_\_\_
9. Signature of person authorized to sign in lieu of the patient (where required)  
\_\_\_\_\_
10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specify date, event, or condition, i.e. termination of treatment)

### Notice to accompany disclosure:

Each disclosure made with the patient's written consent must be accompanied by the following written statement:

This information has been disclosed to you from records protected by Federal confidentiality rules (42 CFR Part 2). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the person to whom it pertains or as otherwise permitted by 42 CFR Part 2. A general authorization for the

release of medical or other information is NOT sufficient for this purpose. The Federal rules restrict any use of the information to criminally investigate or prosecute any alcohol or drug abuse patient.

For more information:

[www.zubsolvrems.com](http://www.zubsolvrems.com)

ZUBSOLV REMS call center (toll-free) 1-877-ZUBSOLV (1-877-982-7658)

Patient Name: \_\_\_\_\_

## Appropriate Use Checklist

### APPROPRIATE USE CHECKLIST: ZUBSOLV®

This checklist is a useful reminder of the safe use conditions and monitoring requirements for prescribing Zubsolv for opioid dependence.

Requirements to address during each patient's appointment include:

- understanding and reinforcement of safe use conditions
- the importance of psychosocial counseling
- screening and monitoring patients to determine progress towards treatment goals

If a patient continues to abuse various drugs or is unresponsive to treatment, including psychosocial intervention, it is important that you assess the need to refer the patient to a specialist and/or a more intensive behavioral treatment environment.

Additional resource: Physician Clinical Support System: <http://pcssb.org/>

**This checklist may be used during the induction period and filed in patient's medical record to document safe use conditions. Once a maintenance dose has been established, use the maintenance checklist.**

Measurement to Ensure Appropriate Use	NOTES:
<b>Date:</b>	
<b>Induction</b>	
<input type="checkbox"/> Verified patient meets diagnostic criteria for opioid dependence	
<input type="checkbox"/> Discussed risks described in professional labeling and Medication Guide with patient	
<input type="checkbox"/> Explained or reviewed conditions of safe storage of medication	
<input type="checkbox"/> Provided induction doses under appropriate supervision	
<input type="checkbox"/> Prescribed limited amount of medication at first visit	
<input type="checkbox"/> Scheduled next visit at interval commensurate with patient stability <ul style="list-style-type: none"><li>• Weekly, or more frequent visits recommended for the first month</li></ul>	

Patient Name: \_\_\_\_\_

**This checklist may be used for visits following the induction period and filed in patient's medical record to document safe use conditions.**

Measurement to Ensure Appropriate Use	NOTES:
<b>Date:</b>	
<b>Visit #:</b>	
<b>Maintenance</b>	
<input type="checkbox"/> Assessed and encouraged patient to take medication as prescribed <ul style="list-style-type: none"> <li>• Consider pill count/dose reconciliation</li> </ul>	
<input type="checkbox"/> Assessed appropriateness of dosage <ul style="list-style-type: none"> <li>• Zubsolv containing 8.5 mg to 11.4 mg buprenorphine combined with naloxone is recommended for maintenance</li> <li>• The need for higher dose should be carefully evaluated</li> </ul>	
<input type="checkbox"/> Conduct urine drug screens as appropriate to assess use of illicit substances	
<input type="checkbox"/> Assessed participation in professional counseling and support services	
<input type="checkbox"/> Assessed whether benefits of treatment with buprenorphine-containing products outweigh risks associated with buprenorphine-containing products	
<input type="checkbox"/> Assessed whether patient is making adequate progress toward treatment goals <ul style="list-style-type: none"> <li>• Considered results of urine drug screens as part of the evidence of the patient complying with the treatment program</li> <li>• Consider referral to more intensive forms of treatment for patients not making progress</li> </ul>	
<input type="checkbox"/> Scheduled next visit at interval commensurate with patient stability <ul style="list-style-type: none"> <li>• Weekly, or more frequent visits are recommended for the first month</li> </ul>	

## IMPORTANT SAFETY INFORMATION

**Subject: Risk Evaluation and Mitigation Strategy (REMS) for Zubsolv<sup>®</sup> for opioid dependence due to the risks of accidental overdose, misuse, and abuse.**

<DATE>

Dear Pharmacist:

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) for Zubsolv. This REMS does not apply to Zubsolv that is dispensed to patients in an Opioid Treatment Program (OTP) under 42 CFR Part 8.

The FDA has determined that a REMS is necessary to ensure that the benefits of Zubsolv for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Zubsolv is indicated for the maintenance treatment of opioid dependence and is used as part of a complete treatment plan, including counseling and psychosocial support.

### **Serious Risks of Zubsolv**

The following key messages need to be communicated to patients about the risks of accidental overdose, misuse, and abuse while taking Zubsolv:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) while taking Zubsolv. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their prescriber
- Instruct patients to keep Zubsolv in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to Zubsolv, medical attention should be sought immediately
- Advise patients that Zubsolv contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their products in a safe place, and to protect them from theft
- Instruct patients never to give Zubsolv to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death
- Advise patients that selling or giving away this medication is against the law

### **Pharmacist Action**

Pharmacists are encouraged to read the enclosed educational brochure entitled *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*. Each time you fill a prescription for Zubsolv, make sure to:

- Verify that the prescription you receive is from a prescriber who is in compliance with the provisions of DATA 2000

- Keep in mind that a limited supply of Zubsolv should be dispensed during the initiation of therapy. This is due to the need of prescribers to closely and frequently assess the patients' needs, their symptoms, and potential risk of misuse, diversion, and abuse
- Provide the Medication Guide to patients each time the medicine is dispensed
- Remind patients who are picking up induction doses to return as directed to the doctor's office so that they can be supervised while taking the medication
- Provide appropriate patient counseling on safe use of Zubsolv
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

### **Medication Guide**

The Zubsolv REMS includes a Medication Guide on the safe and effective use of Zubsolv, and the importance of participating in psychosocial support with important information to be reviewed with patients. It is important that you provide a Medication Guide to your patients or their caregivers with each dispensing and encourage them to read it.

### **Reporting Adverse Events**

To report SUSPECTED ADVERSE EVENTS contact:

- Orexo US, Inc. by phone at 1-888-ZUBSOLV (1-888-982-7658) or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This letter is not a comprehensive description of the risks associated with the use of Zubsolv. Additional important safety information can be found in the ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*** educational brochure and Full Prescribing Information.

Additional copies of the educational brochure, Full Prescribing Information, and Medication Guide for Zubsolv, can be obtained at [www.zubsolvrems.com](http://www.zubsolvrems.com) or by contacting the toll-free call center at 1-877-ZUBSOLV (1-877-982-7658).

Sincerely,

Peter Hjelmström, MD, PhD, Assoc Prof  
Chief Medical Officer  
Head of Clinical Development

*Enclosures: Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*

# Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists

Zubsolv<sup>®</sup>

## I. Introduction

The purpose of this brochure is to provide pharmacists with information about the Risk Evaluation and Mitigation Strategy (REMS) for Zubsolv, a buprenorphine containing product, and the important safety issues and messages needed to counsel patients about its safe use. 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.

### **What are buprenorphine-containing products?**

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with a second ingredient, naloxone.

Buprenorphine-containing products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction.

Some buprenorphine products are combined with second active ingredient, naloxone HCl, intended to deter individuals from abusing buprenorphine-containing products by the intravenous route. Products containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence.

Buprenorphine-containing products are used as part of a complete treatment plan, including counseling and psychosocial support.

### **What are the primary differences among the buprenorphine products that contain naloxone?**

The primary differences are the available dosage strengths, recommended doses, and formulations. The available dosage strengths and recommended doses vary based on the bioavailability for each product (i.e, how much of the buprenorphine is absorbed after administration). Suboxone<sup>1</sup> sublingual tablets, including generic equivalents, are available as 2 mg buprenorphine/0.5 mg naloxone and 8 mg buprenorphine/2 mg naloxone dosage strengths. Zubsolv sublingual tablets are available as 1.4 mg buprenorphine/0.36 mg naloxone and 5.7 mg buprenorphine/1.4 mg naloxone dosage strengths. Buprenorphine/naloxone sublingual film is available as 2 mg buprenorphine/0.5 mg naloxone, 4 mg buprenorphine/1 mg naloxone, 8 mg buprenorphine/2 mg naloxone, and 12 mg buprenorphine/3 mg naloxone dosage strengths.

Patients being switched between different formulations should be started on the corresponding dose (as shown in the table below) compared to the previously administered product. Patients

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<sup>1</sup>Buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone<sup>®</sup> are covered under the Suboxone REMS program.

should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated<sup>2</sup>.

<b>Corresponding doses of buprenorphine products that contain naloxone</b>		
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

### **When are buprenorphine-containing products prescribed?**

Buprenorphine with naloxone is indicated for the maintenance treatment of opioid dependence and is preferred for unsupervised administration.

Buprenorphine alone is preferred for use during induction. Therefore, while you may see prescriptions for small amounts of buprenorphine alone presented for induction doses, you should expect the majority of prescriptions to be for buprenorphine with naloxone.

Buprenorphine-containing products are controlled as Schedule III narcotics under the Controlled Substances Act.

Full Prescribing Information for Zubsolv can be found at [www.zubsolvrems.com](http://www.zubsolvrems.com).

## **II. REMS – Risk Evaluation and Mitigation Strategy**

### **What is a REMS?**

A REMS is a strategy to manage a known or potential risk associated with a drug. A REMS can include, among other strategies, a Medication Guide, a communication plan, and elements to assure safe use.

### **Is there a REMS for Zubsolv?**

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with Zubsolv outweigh the potential risks, particularly risks of accidental overdose, misuse, and abuse.

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<sup>2</sup> Note that, although the nominal Suboxone sublingual film doses are the same as the Suboxone sublingual tablets and generic equivalent tablets, not all strengths and combinations of the films are bioequivalent to the tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

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 the use of buprenorphine-containing products

### **What is my role with regard to the Zubsolv REMS?**

As part of the REMS, pharmacists dispensing Zubsolv for opioid dependence must supply a Medication Guide with each prescription. The Medication Guide will be provided with the product and is also available by going online to [www.zubsolvrems.com](http://www.zubsolvrems.com) or calling 1-877-ZUBSOLV (1-877-982-7658).

**What is the role of the pharmacist in ensuring safe use of buprenorphine-containing products?** As a pharmacist, you will play an important role in ensuring that buprenorphine-containing products are used safely and appropriately. Each time you fill a prescription for a buprenorphine-containing product, make sure to:

- Verify that the prescription you receive is from a prescriber who is in compliance with the provisions of DATA 2000
- Keep in mind that a limited supply of buprenorphine-containing products should be dispensed during the initiation of therapy. This is due to the need of prescribers to closely and frequently assess the patients' needs, their symptoms, and potential risk of misuse, diversion, and abuse
- Provide the Medication Guide to patients each time the medicine is dispensed
- Remind patients who are picking up induction doses to return as directed to the doctor's office so that they can be supervised while taking the medication
- Provide appropriate patient counseling on safe use of buprenorphine-containing products (see Section VI. Patient Information).
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

## **III. Highlighted Important Safety Information for Buprenorphine-Containing Products**

This section of the brochure highlights important safety information to consider when prescribing or dispensing buprenorphine-containing products, including Zubsolv. **Please refer to the Full Prescribing Information (FPI) for detailed safety-related information for Zubsolv.**

### ***Abuse Potential of Buprenorphine-Containing Products***

#### **Are buprenorphine-containing products abusable?**

Yes, buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when dispensing buprenorphine in

situations when there is a concern about an increased risk of misuse, abuse, or diversion. All healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant use of buprenorphine and alcohol and other substances, especially benzodiazepines.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

Due to the partial agonist properties of buprenorphine, buprenorphine-containing products may precipitate opioid withdrawal signs and symptoms in persons dependent on full opioid agonists if administered before the agonist effects of the opioid have subsided. However, buprenorphine products that contain naloxone are highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Therefore, to discourage misuse or abuse, it is highly recommended that, for unsupervised administration, buprenorphine with naloxone rather than buprenorphine alone is prescribed whenever feasible after induction.

However, pharmacists should also be aware that some opioid-dependent persons can and do abuse buprenorphine/naloxone combinations by the intravenous or intranasal route, in particular opioid-dependent persons with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine.

### **Can buprenorphine-containing products cause dependence?**

Yes, buprenorphine is a partial agonist at the mu-opioid receptor. Chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. If cessation of therapy is indicated, it is appropriate to taper the buprenorphine dose, rather than abruptly discontinue the medication. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing buprenorphine in situations where there is an increased concern about the possibility of misuse, diversion, or abuse.

### **How can patients prevent accidental exposure to buprenorphine-containing products in children?**

Patients should be instructed to keep buprenorphine-containing products in a secure place, out of the sight and reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed accidentally to a buprenorphine-containing product, seek immediate urgent medical attention.

## **What is an appropriate medical response to an overdose on a buprenorphine-containing product?**

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone hydrochloride may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

### ***Contraindications***

- Hypersensitivity to buprenorphine and, in the case of combination products, naloxone

### ***Warnings and Precautions***

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol)
- Consider dose reduction of CNS depressants, buprenorphine-containing products, or both in situations of concomitant prescription
- Store buprenorphine-containing products safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events
- Do not administer buprenorphine-containing products to patients with known hypersensitivity to buprenorphine or, in the case of combination products, naloxone
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of buprenorphine-containing products by individuals physically dependent on full opioid agonists before the agonist effects of other opioids have subsided, particularly buprenorphine-containing products that also contain naloxone
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- Buprenorphine-containing products indicated for the treatment of opioid dependence are not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose
- Caution patients about the risk of driving or operating hazardous machinery

## *Adverse Reactions*

### **What are the most commonly observed adverse events of buprenorphine-containing products?**

- Adverse events most commonly observed with buprenorphine-containing products are: headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. For a complete list of potential adverse events associated with buprenorphine-containing products, please see the Full Prescribing Information.
- To report SUSPECTED ADVERSE REACTIONS contact:
  - The manufacturer of the product taken or
  - FDA MedWatch program by phone at 1-800-FDA-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

## *Drug Interactions*

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing
- Use caution in prescribing buprenorphine-containing products for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse

## *Use in Specific Populations*

- Buprenorphine-containing products are not indicated for use during pregnancy unless potential benefit justifies potential risk
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking buprenorphine-containing products
- Safety and effectiveness of buprenorphine-containing products in patients below the age of 16 have not been established
- Administer buprenorphine-containing products with caution to elderly or debilitated patients
- Administer buprenorphine-containing products with caution in patients with liver dysfunction

## **IV. Dispensing Prescriptions for Buprenorphine-Containing Products**

This section discusses important information to consider before filling prescriptions for buprenorphine-containing products.

### **Who is qualified to prescribe buprenorphine-containing products?**

A Federal law, Drug Addiction Treatment Act of 2000 (DATA 2000), limits office-based use of buprenorphine-containing products to prescribers who have met qualifications to receive a waiver.

### **How can I be sure a prescriber is qualified to prescribe buprenorphine-containing products?**

Pharmacists can verify the validity of a prescriber's DATA 2000 waiver by calling 1-866BUP-CSAT (1-866-287-2728), or e-mailing [info@buprenorphine.samhsa.gov](mailto:info@buprenorphine.samhsa.gov).

DEA regulations require that this number, along with the existing DEA registration number, is included on all prescriptions for buprenorphine-containing products for the treatment of opioid dependence.

### **What if I get a prescription from a doctor who does not have a special DEA identification number?**

Call that prescriber for clarification and confirm that the prescriber has submitted a Notification of Intent form to SAMHSA. The DEA has developed regulations that require this number, along with the prescriber's existing DEA registration number, to be included on all prescriptions issued for the treatment of opioid dependence.

Most prescribers will make arrangements to obtain the identification number before prescribing buprenorphine-containing products, but in rare cases, a prescriber may need to write a prescription before the number has been issued. This is allowed under DATA 2000, provided the prescriber has notified SAMHSA of his/her intention to begin treating a patient immediately.

### **How can I verify that a prescription is legitimate?**

According to federal law, pharmacists and prescribers jointly share legal responsibility for the legitimacy of a prescription. Communication between you and the prescriber is vital to ensure the validity of each prescription you're asked to fill.

However, even if you determine that an individual prescription is legitimate, you should still be aware of other means by which patients may attempt to divert their prescriptions. For example, an opioid user may present themselves to 2 or more qualified prescribers and therefore, receive multiple prescriptions for buprenorphine-containing products. If a patient brings you more than 1 prescription covering the same therapeutic period, you have a legal duty to recognize that they may not be for therapeutic use. You should contact each prescriber for verification and notify them of the additional pending prescription.

## **What should I do if I am seeing prescriptions from a single prescriber that seem to exceed the patient limit?**

Prescribers agree to treat no more than 30 patients at a time during the first year of providing buprenorphine treatment. After a year, their patient limit may be increased to 100 patients.

If you are concerned about the validity of the prescription for any reason, including exceeding the patient limit, begin by contacting the prescriber for clarification. In some cases, the prescriber needs the patient's consent to discuss specific patient issues.

You can also contact: SAMHSA/CSAT at 1-866-BUP-CSAT (1-866-287-2728) or by email: [info@buprenorphine.samhsa.gov](mailto:info@buprenorphine.samhsa.gov); DEA ([www.deadiversion.usdoj.gov](http://www.deadiversion.usdoj.gov)); and the State Board of Medicine (a list of contact numbers may be found at this website: [www.fsmb.org/directory\\_smb.html](http://www.fsmb.org/directory_smb.html)).

## **Are there confidentiality issues I should be aware of related to substance abuse treatment?**

People with opioid dependence are more likely to seek and continue with treatment when they know their treatment will be held in strict confidence.

For this reason, federal regulations protect the privacy of patients' medical information, namely Title 42 Part 2 of the Code of Federal Regulations (42 CFR Part 2) and the Health Insurance Portability and Accountability Act (HIPAA).

42 CFR Part 2 states that any patient-identifying information pertaining to treatment for substance abuse must be handled with a greater degree of confidentiality than patients' general medical information.

Under 42 CFR Part 2, before a prescriber can disclose any information to a third party about a patient's treatment for substance abuse, that prescriber must first obtain the patient's signed consent.

When a prescriber directly transmits a prescription for a buprenorphine-containing product to your pharmacy, any redisclosure of that patient-identifying information by the *pharmacy* is prohibited without the patient's signed consent.

According to 42 CFR Part 2, the following elements are required for a consent form to be considered valid:

- Patient's name, prescriber's name, pharmacist's name
- Purpose of the disclosure; recipient of the disclosure
- What information will be released
- An indication that the patient understands he/she can revoke this consent at any time and that this revocation can be verbal
- The date and terms under which the consent expires
- Patient's dated signature

To learn more about these regulations, visit the SAMHSA website, <http://www.samhsa.gov/healthprivacy/>, or call 1-866-BUP-CSAT (1-866-287-2728).

**Are there any special storage, record keeping, or other requirements associated with buprenorphine-containing products?**

Buprenorphine-containing products are Schedule III controlled substances; therefore, buprenorphine-containing products are subject to certain federal regulations covering areas such as record keeping, inventory, proper dispensing and disposal. These are explained in the DEA’s Pharmacist’s Manual, which can be found at [www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html](http://www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html). Many states have their own additional requirements for pharmacists dispensing controlled substances. Be sure to check with the appropriate authority in your state. For more information, visit the website of the National Association of Boards of Pharmacy at [www.nabp.net](http://www.nabp.net) for links to individual state boards of pharmacy.

**V. Supplying and Administering Buprenorphine-Containing Products**

**How are buprenorphine-containing products supplied?**

Subutex sublingual tablets, including generic equivalents	2 mg buprenorphine	8 mg buprenorphine		
Subxone sublingual tablets, including generic equivalents	2 mg buprenorphine / 0.5 mg naloxone	8 mg buprenorphine / 2 mg naloxone		
Zubsolv sublingual tablets	1.4 mg buprenorphine / 0.36 mg naloxone	5.7 mg buprenorphine / 1.4 mg naloxone		
Suboxone sublingual film	2 mg buprenorphine / 0.5 mg naloxone	4mg buprenorphine / 1 mg naloxone	8mg buprenorphine / 2 mg naloxone	12 mg buprenorphine / 3 mg naloxone

**How should buprenorphine-containing products be administered?**

Tablets should be placed under the tongue until they are dissolved. For doses requiring the use of more than 2 tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than 2 tablets comfortably), place 2 tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve;

swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

## **VI. Patient Information**

### **What information should I relay to patients about the safe use of buprenorphine-containing products?**

The safety concerns related to the use of buprenorphine-containing products includes, but are not limited to, the following:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking buprenorphine-containing products. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their prescriber
- Instruct patients to keep buprenorphine-containing products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to buprenorphine-containing products, medical attention should be sought immediately
- Advise patients that buprenorphine-containing products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their products in a safe place and to protect them from theft
- Instruct patients never to give buprenorphine-containing products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death
- Advise patients that selling or giving away buprenorphine-containing products is against the law
- Caution patients that buprenorphine-containing products may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken, especially during drug induction and dose adjustments and until they are reasonably certain that buprenorphine-containing products do not adversely affect their ability to engage in such activities
- Advise patients not to change the dose of buprenorphine-containing products without consulting their prescriber
- Advise patients to take buprenorphine-containing products once a day as directed
- Inform patients that buprenorphine-containing products can cause drug dependence of the opioid type. Withdrawal signs and symptoms may occur when the medication is discontinued
- Advise patients seeking to discontinue treatment with buprenorphine-containing products for opioid dependence to work closely with their prescriber on a tapering schedule, and apprise of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment
- Caution patients that, like other opioids, buprenorphine-containing products may produce orthostatic hypotension in ambulatory individuals
- Ask patients if other prescription medications, over-the-counter medications or herbal preparations are prescribed or are currently being used

- Advise patients who become pregnant, or are planning to become pregnant, to consult their prescriber regarding the possible effects secondary to using buprenorphine-containing products during pregnancy
- Warn patients that buprenorphine passes into breast milk and breast-feeding is therefore not advised in mothers treated with buprenorphine-containing products
- Ask patients to inform their family members or other appropriate individuals that, in the event of emergency, the treating prescriber or emergency department staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with buprenorphine-containing products
- Instruct patients to dispose of unused buprenorphine-containing products as soon as it is no longer needed. Unused tablets should be flushed down the toilet.

## **VII. Where can I get more information on treating opioid addiction with buprenorphine-containing products?**

Refer to the package insert of the product you are dispensing for full information on the adverse reactions seen during the clinical trials using buprenorphine for opioid dependence treatment

General information about buprenorphine treatment and the treatment of addiction are available through numerous sources, including but not limited to:

- SAMHSA website ([www.dpt.samhsa.gov](http://www.dpt.samhsa.gov))
- American Society of Addiction Medicine website ([www.asam.org](http://www.asam.org))
- American Academy of Addiction Psychiatry website ([www.aaap.org](http://www.aaap.org))

For more information:

[www.zubsolvrems.com](http://www.zubsolvrems.com)

ZUBSOLV REMS call center (toll-free) 1-877-ZUBSOLV (1-877-982-7658)

# Zubsolv<sup>®</sup> REMS

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## The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for Zubsolv sublingual tablets

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of a drug outweigh its risks.

The purpose of the Zubsolv REMS program is to inform healthcare professionals and patients about the safe use conditions and serious risks, including accidental overdose, misuse, and abuse, associated with Zubsolv indicated for the maintenance treatment of opioid dependence.

### **Prescribers should:**

- **Verify** that patients meet diagnostic criteria for opioid dependence
- **Counsel** patients and/or their caregivers on safe use of the product, including appropriate storage and disposal, and risks associated with treatment, at each visit
- **Monitor and document** safe use conditions for each patient by using the [Appropriate Use Checklist](#) (or by other means specific to office practice)
- **Assess** appropriateness of treatment and adequate progress towards treatment goals for each patient

To prescribe Zubsolv, a prescriber must be certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). For certification information, [click here](#).

### **Materials for Prescribers:**

[Dear Prescriber Letter](#)

[Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#)

[Appropriate Use Checklist](#)

### **Materials for Pharmacists:**

[Dear Pharmacist Letter](#)

[Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists](#)

### **Materials for Patients:**

[Medication Guides](#)

For more information or to receive print copies of the materials, please call: **1-877-ZUBSOLV (1-877-982-7658)**.

This REMS does not apply to buprenorphine-containing products indicated for the treatment of pain or for Zubsolv dispensed to patients admitted to Opioid Treatment Programs (OTP) under 42 CFR part 8.

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## Important Safety Information

Zubsolv, a buprenorphine-containing product combined with naloxone, is delivered by the oral transmucosal route and is indicated for the maintenance treatment of opioid dependence as part of a comprehensive treatment plan to include counseling and psychosocial support. Treatment must be initiated under the direction of prescribers qualified under the Drug Addiction Treatment Act of 2000.

Buprenorphine-containing products must not be used by patients with hypersensitivity to buprenorphine, and/or naloxone in the case of combination products.

Buprenorphine-containing products can be abused in a manner similar to other opioids, legal or illicit. Clinical monitoring appropriate to the patient's level of stability is essential.

Children who ingest buprenorphine-containing products can have severe, possibly fatal, respiratory depression. Emergency medical care is critical. Keep buprenorphine-containing products out of the sight and reach of children.

Buprenorphine-containing products can cause serious life-threatening respiratory depression and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other central nervous system (CNS) depressants (i.e., sedatives, tranquilizers, or alcohol). It is extremely dangerous to self-administer nonprescribed benzodiazepines or other CNS depressants while taking buprenorphine-containing products. When buprenorphine-containing products are taken together with CNS depressants, dose reduction of either product(s) should be considered.

Death has been reported in nontolerant, nondependent individuals who received a 2 mg dose for analgesia. The products covered under this REMS are not appropriate for use as an analgesic.

Chronic use of buprenorphine can cause physical dependence. A sudden or rapid decrease in dose may result in an opioid withdrawal syndrome that is typically milder than seen with full agonists (e.g., heroin, hydrocodone, methadone, morphine, oxycodone) and may be delayed in onset. Intravenous misuse or taking buprenorphine-containing products before the effects of full-agonist opioids have subsided is highly likely to cause opioid withdrawal symptoms.

Liver function should be monitored before and during treatment.

Use of buprenorphine-containing products in pregnant women or during breast-feeding should only be considered if the potential benefit justifies the potential risk. Neonatal withdrawal has been reported.

Caution should be exercised when driving vehicles or operating hazardous machinery, especially during dose adjustment.

Adverse events most commonly observed with the sublingual administration of buprenorphine during clinical trials and post-marketing experience are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. An additional adverse event among those most commonly observed with sublingual administration of buprenorphine/naloxone formulations is peripheral edema.

Cytolytic hepatitis, jaundice, and allergic reactions, including anaphylactic shock, have been reported.

This is not a complete list of potential adverse events associated with buprenorphine-containing products. Please see the [Full Prescribing Information](#) of Zubsolv for a complete list.

For more information about the Zubsolv REMS, including all program materials and instructions call 1-877-ZUBSOLV (1-877-982-7658).

To report SUSPECTED ADVERSE EVENTS, contact:

- Orexo US, Inc. by phone at 1-888-ZUBSOLV (1-888-982-7658) or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

Please see the [Full Prescribing Information](#) and [Medication Guide](#) for Zubsolv.

## Materials for Prescribers:

[Dear Prescriber Letter](#)

[Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#)

[Appropriate Use Checklist](#)

## Materials for Pharmacists:

[Dear Pharmacist Letter](#)

[Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists](#)

## Materials for Patients:

[Medication Guides](#)

For more information or to receive print copies of the materials, please call: **1-877-ZUBSOLV (1-877-982-7658)**.

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## Getting Certified

Under the Drug Addiction Treatment Act of 2000 (DATA 2000), prescription use of buprenorphine-containing products in the treatment of opioid dependence is limited to prescribers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

To become certified to prescribe buprenorphine-containing products, you will need to follow certification guidelines set by DATA 2000.

Detailed information about DATA 2000, qualifications, notifying SAMHSA, and the general prescriber waiver process can be found at [buprenorphine.samhsa.gov](http://buprenorphine.samhsa.gov), or by contacting SAMHSA directly:

### **SAMHSA Buprenorphine Information Center**

Phone: 1-866-287-2729 (866-BUP-CSAT)

E-mail: [info@buprenorphine.samhsa.gov](mailto:info@buprenorphine.samhsa.gov)

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This REMS does not apply to buprenorphine-containing products indicated for the treatment of pain or for Zubsolv dispensed to patients admitted to Opioid Treatment Programs (OTP) under 42 CFR part 8.

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/s/  
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BOB A RAPPAPORT  
07/03/2013