

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205637Orig1s000

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

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

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

NDA/BLA #s:	205637
Products:	Bunavail (buprenorphine and naloxone) buccal film
SPONSOR:	Biodelivery Sciences International
FROM:	Judith A. Racoosin, MD, MPH
DATE:	June 3, 2014

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

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

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

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

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

A REMS for Suboxone (buprenorphine/naloxone) film was approved in August 2010. A REMS for Suboxone (buprenorphine/naloxone) and Subutex (buprenorphine) tablets was approved in December 2011. The BTOD (Buprenorphine for the Treatment of Opioid Dependence) REMS was approved in February 2013 for generic oral transmucosal buprenorphine products. Zubsolv, a buprenorphine/naloxone sublingual tablet with a different dosing regimen than Suboxone, was approved on July 3, 2013 and joined the BTOD REMS on September 4, 2013.

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

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

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

hepatotoxicity, allergic reactions, and accidental pediatric exposures which are potentially lethal. Abuse and accidental overdose are common in the population, as are hepatic events attributable to blood-borne illnesses and use of other hepatotoxic substances.

F. Bunavail (buprenorphine and naloxone) is not a new molecular entity.

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

The elements of the REMS include:

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

This REMS will use a waiver-granted shared system, specifically the BTOD (Buprenorphine for the Treatment of Opioid Dependence) REMS, for the elements to assure safe use, implementation system, and the REMS assessments.

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/s/

JUDITH A RACOOSIN
06/05/2014

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

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	June 5, 2014
Reviewer(s):	Jamie Wilkins Parker, Pharm.D. Risk Management Analyst Division of Risk Management
Team Leader:	Kim Lehrfeld, PharmD, BCPS Division of Risk Management
Division Director	Claudia Manzo, PharmD Division of Risk Management
Drug Name(s):	Bunavail (Buprenorphine/Naloxone) Buccal Film
Therapeutic Class:	Opioid partial agonist-antagonist
Dosage and Route:	(b) (4) 2.1/0.348 mg, 4.2/0.696 mg and 6.3/1.044 mg buccal films
Application Type/Number:	NDA 205637
Submission Number:	Sequence No. 0033
Applicant/sponsor:	Biodelivery Sciences International, Inc.
OSE RCM #:	2013-2023

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

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1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of the proposed Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS submitted by Bidelivery Sciences International, Inc. (BDSI) on November 22, 2013. The Sponsor is a member of the Buprenorphine Products Manufacturers Group (BPMG) and will market their product under the single, shared system (SSS) Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS.

1.1 BACKGROUND

Buprenorphine, a semi-synthetic opioid, is a partial mu-opioid receptor agonist and a kappa-opioid receptor antagonist. The transmucosal sublingual formulations are indicated for the treatment of opioid dependence. In combination with naloxone, it is indicated for maintenance (and some formulations induction of) treatment of opioid dependence.

As described in DRISKs February 21, 2013 REMS review, FDA determined that buprenorphine-containing transmucosal products for opioid dependence were required to have a REMS to ensure that the benefits of the drug outweighed the increased risks of misuse, abuse, and overdose. The BTOD REMS was originally approved on February 22, 2013.

The most recently approved BTOD REMS (last modified September 4, 2013) consists of a Medication Guide, elements to assure safe use, and implementation system.

The goals of this 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

Bunavail (buprenorphine and naloxone buccal film), an opioid partial agonist-antagonist, is proposed by the Sponsor for the once daily maintenance treatment of opioid dependence. The Sponsor's product is a mucoadhesive film with one side containing buprenorphine and the other containing naloxone. The Sponsor's NDA includes the following proposed buccal film doses: (b) (4) 2.1/0.348 mg, 4.2/0.696 mg and 6.3/1.044 mg. It is to be noted that the concentration of drug product is the same for all films; the dose is determined by the film size.

Buprenorphine and naloxone is currently available in sublingual tablet as well as film form.

1.2 SAFETY CONCERNS

The Sponsor has demonstrated the efficacy of all strengths of Bunavail with the exception of the (b) (4) mg dose, as required by the Agency, relying on the previous finding of efficacy for Suboxone and has provided a bridge between Suboxone and

Bunavail based on clinical pharmacology data.

(b) (4)

The safety data provided by the Sponsor demonstrated that there were no adverse events identified that indicate a unique safety issue with the proposed formulation¹. No new or unexpected safety signals were identified during review of this NDA. Known adverse events associated with buprenorphine also seen with this product include lethargy, headache, nasopharyngitis, and fatigue.

1.3 REGULATORY HISTORY

As described in DRISKS February 21, 2013 REMS review, FDA determined that buprenorphine-containing transmucosal products for opioid dependence were required to have a REMS to ensure that the benefits of the drug outweighed the increased risks of misuse, abuse, and overdose. The BTOD REMS was originally approved on February 22, 2013 and modified on September 4, 2013.

On July 31, 2013, BDSI submitted NDA 205637 for Bunavail as a 505(b)2 application, relying on prior findings of safety and efficacy for Suboxone (buprenorphine/naloxone) tablets. In the NDA submission, the Sponsor included a REMS proposal, which, at the time was the most up to date BTOD REMS.

On November 22, 2013, BDSI submitted a revised REMS, which incorporated their product's information in the BTOD REMS which was approved on September 4, 2013.

On May 15, 2014, DAAAP's Cross-Discipline Team Leader's (CDTL) review of Bunavail recommended approval of Bunavail (C. Winchell, May 15, 2014). The following summarizes the rationale for approval:

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

On May 23, 2014, DAAAP provided the SCPI² to the Sponsor, and on May 27, 2014 informed them to resubmit the revised REMS materials that reflect the SCPI within 5 business days.

¹ Primary Clinical Review, P. Horn. 5/1/2014

² Substantially Complete Package Insert Labeling

On June 5, 2014, the Sponsor amended the proposed REMS (Sequence No. 0033).

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following submissions, listed by date received, were reviewed from NDA 205637 for the proposed BTOD REMS:

- 07/31/2013 Proposed REMS (Sequence No. 0000)
 - o 11/22/2013: Amendment 1 (Sequence No. 0008)
 - o 06/05/2014: Amendment 2 (Sequence No. 0033)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Patient Labeling Medication Guide Review (dated May 23, 2014)
- DAAAP Primary Clinical Review (dated May 1, 2014)
- DAAAP Cross-Discipline Team Leader Review (dated May 15, 2014)
- BTOD REMS; last modified September, 4 2013

3 RESULTS OF REVIEW OF BTOD RISK EVALUATION AND MITIGATION STRATEGY MODIFICATION

The focus of the review of the proposed REMS for Bunavail was to incorporate Bunavail's information into the approved BTOD REMS.

Prescriber and Pharmacist Brochures:

- I. Incorporated Bunavail information into the following 2 tables in the brochures:
Corresponding doses of buprenorphine products that contain naloxone and the How are buprenorphine products supplied?

Corresponding doses of buprenorphine products that contain naloxone			
Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual film	Zubsolv sublingual tablets	Bunavail buccal films
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	
	4 mg buprenorphine/ 1 mg naloxone		2.1 mg buprenorphine/ 0.3 mg naloxone

8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone
	12 mg buprenorphine/ 3 mg naloxone		6.3 mg buprenorphine/ 1 mg naloxone

How are buprenorphine-containing products supplied?

Subutex sublingual tablets, including generic equivalents	2 mg buprenorphine	8 mg buprenorphine		
Suboxone 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
Bunavail buccal film		2.1 mg buprenorphine / 0.3 mg naloxone	4.2 mg buprenorphine / 0.7 mg naloxone	6.3 mg buprenorphine / 1 mg naloxone

- II. Incorporated the following use instructions for Bunavail into the *Dosing and Administration of Buprenorphine-containing Product- How should buprenorphine with or without naloxone be administered?* section of the brochures:

For Bunavail administration, the patient should use the tongue to wet the inside of the cheek or rinse the mouth with water to moisten the area immediately before placement of Bunavail; open the Bunavail package immediately prior to use as indicated by the instructions; place the Bunavail film near the tip of a dry finger with the text facing up; place the side of the Bunavail film with the text against the inside of the cheek; press and hold the film in place for 5 seconds. Bunavail film(s) adhere to the moist buccal mucosa and should stay in place after this period. If multiple films need to be administered, the patient should immediately apply the next film. Note that when two films are required for one dose, the patient should place one film on the inside of each cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time. The patient should be instructed to avoid manipulating the film(s) with their tongue or finger(s) and avoid drinking or eating food until the film(s) dissolve.

BTOD REMS Update Prescriber and Pharmacist Letter

BDSI proposes to distribute a one-time letter to Pharmacists and Prescribers in order to inform them of the inclusion of Bunavail to the BTOD REMS.

Reviewer's Comments: A letter of this type was also sent upon the approval and addition of Zubsolv to the BTOD REMS. It is appropriate since the addition of an NDA product that does not have 1:1 mg dose correspondence to the existing products in the REMS is important for HCP to understand.

BTOD REMS Website

Inclusion of Bunavail to the BTOD REMS Website was submitted to the Application.

4 DISCUSSION

As another addition to the buprenorphine/naloxone family of products to treat opioid addiction, Bunavail has shown via biowaiver to be safe and effective at 3 of its 4 proposed doses. The Bunavail film is unique as the concentration of buprenorphine and naloxone is consistent through all of the films; the strength is actually acquired by way of the size of the film itself. This did not present any issue during clinical trials.

As this is a combination buprenorphine/naloxone product for the treatment of opioid dependence and thus poses the same risks of accidental overdose, misuse, and abuse as the existing products with this combination of medications and indication, if approved, will be a part of the BTOD REMS. DRISK agrees with the addition of Bunavail to the approved BTOD REMS.

In April 2014, the currently marketed buprenorphine/naloxone product, Suboxone Film's REMS was updated to include a new indication for induction of opioid treatment for

patients addicted to short acting opioids or heroin, as well as updated language regarding use in patients with hepatic impairment. The information contained in the Suboxone Film REMS is important safety information which must be incorporated into the waiver-granted BTOD REMS materials, and thus the BTOD REMS will undergo a modification to include this updated information.

If approved during the current review cycle, for administrative reasons, the REMS materials approved for Bunavail will not include the information about induction or hepatic effects, as the BTOD group will be concurrently modifying its REMS materials to include this information, and thus Bunavail's product information as well as the other updated safety information will be incorporated into the same modification. From a practical standpoint, materials will not actually be created or distributed without this information because the BTOD group will be immediately notified and the changes will be rapidly incorporated into the group's materials.

5 CONCLUSION

In conclusion, the BTOD REMS to incorporate the approval for Bunavail (Buprenorphine/Naloxone) Buccal Film, received July 31, 2013, and amended on November 22, 2013 and June 5, 2014, contains the appropriate and agreed upon revisions on the REMS appended materials as stipulated by the Agency. The REMS Supporting Document contains the one-time letter to inform health-care providers of the approval of Bunavail. The timetable for submission of assessments of the REMS and the REMS assessment plan will remain the same as that approved on September 4, 2013.

Therefore, the modified BTOD REMS is acceptable to the Office of Surveillance and Epidemiology, the Division of Risk Management.

6 RECOMMENDATIONS

The OSE, DRISK recommends approval of the REMS Modification BTOD REMS June 5, 2014 and appended to this review.

ATTACHMENTS

1. REMS Document
2. Appropriate Use Checklist
3. Dear Pharmacist Letter
4. Dear Prescriber Letter
5. Pharmacist Brochure
6. Prescriber Brochure
7. BTOD REMS Website

Initial REMS approval: 02/2013
Most Recent Modification: 06/2014

Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD)
Risk Evaluation and Mitigation Strategy (REMS)

This REMS applies to buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence (hereinafter, “buprenorphine-containing products”). This REMS does not apply to buprenorphine-containing products that are dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

I. GOALS

The goals of the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) 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 or Patient Package Insert

A Medication Guide for Trade name (MG) will be dispensed with each prescription for a buprenorphine-containing product in accordance with 21CFR208.24.

The Medication Guides for buprenorphine-containing products are part of the BTOD REMS and will be available through the BTOD REMS website (www.btodrems.com).

B. Elements to Assure Safe Use

1. Safe use conditions

- a. Buprenorphine-containing products 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. Sponsors of this waiver-granted shared REMS (BTOD Sponsors) will ensure that within 60 days of FDA approval of the BTOD 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. BTOD Sponsors 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, BTOD Sponsors will ensure that within 60 days of FDA approval of the BTOD 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. BTOD Sponsors will make the letters and all materials that are appended to the letters available through its toll-free information line, through BTOD REMS specialists and on the BTOD REMS website.
- g. On a monthly basis, the BTOD 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 BTOD REMS specialists will create awareness of the program, confirm that REMS materials have been received by the prescriber, and confirm understanding of the BTOD REMS requirements.
 2. The BTOD REMS specialists will mail a copy of the REMS materials to prescribers who did not receive or request the REMS materials.
 3. The BTOD REMS specialists will offer to provide additional follow-up information. If further follow-up is requested, the BTOD REMS specialist will offer the following options:
 - Option I: A BTOD REMS specialist will provide a live online meeting to review BTOD REMS requirements
 - Option II: A BTOD REMS specialist will provide a field visit to review BTOD REMS requirements

2. Monitoring

- a. Each patient using a buprenorphine-containing product 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 BTOD 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"
- BTOD REMS Website (www.btodrems.com)

C. Implementation System

BTOD Sponsors 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 Section B 1 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 BTOD REMS, if the goals of the REMS are not being met.

D. Timetable for Submission of Assessments

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

**APPROPRIATE USE CHECKLIST:
BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS FOR OPIOID
DEPENDENCE**

This checklist is a useful reminder of the safe use conditions and monitoring requirements for prescribing buprenorphine-containing transmucosal products 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:
Date:	
Induction	
☐ Verified patient meets diagnostic criteria for opioid dependence	
☐ Discussed risks described in professional labeling and Medication Guide with patient	
☐ Explained or reviewed conditions of safe storage of medication	
☐ Provided induction doses under appropriate supervision	
☐ Prescribed limited amount of medication at first visit	
☐ Scheduled next visit at interval commensurate with patient stability • Weekly, or more frequent visits recommended for the first month	

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:
Date:	
Visit #:	
Maintenance	
☐ Assessed and encouraged patient to take medication as prescribed • Consider pill count/dose reconciliation	
☐ Assessed appropriateness of dosage • Buprenorphine combined with naloxone is recommended for maintenance: • Generic formulations of Suboxone®: doses ranging from 12 mg to 16 mg of buprenorphine are recommended for maintenance • Zubsolv®: doses ranging from 8.5 mg to 11.4 mg buprenorphine are recommended for maintenance • Bunavail™: a target dose of 8.4 mg of buprenorphine is recommended for maintenance • Doses higher than this should be an exception • The need for higher dose should be carefully evaluated	
☐ Conduct urine drug screens as appropriate to assess use of illicit substances	
☐ Assessed participation in professional counseling and support services	
☐ Assessed whether benefits of treatment with buprenorphine-containing products outweigh risks associated with buprenorphine-containing products	
☐ Assessed whether patient is making adequate progress toward treatment goals • Considered results of urine drug screens as part of the evidence of the patient complying with the treatment program • Consider referral to more intensive forms of treatment for patients not making progress	

☐ Scheduled next visit at interval commensurate with patient stability • Weekly, or more frequent visits are recommended for the first month	
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Dear Pharmacist Letter

IMPORTANT SAFETY INFORMATION

Subject: Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing transmucosal products for opioid dependence due to their 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) called the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS program. This REMS does not apply to buprenorphine-containing products that are 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 buprenorphine-containing transmucosal products for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction. Products containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. These products are used as part of a complete treatment plan, including counseling and psychosocial support.

Serious Risks of Buprenorphine-containing Products

The following key messages need to be communicated to patients about the risks of accidental overdose, misuse, and abuse while taking products covered under the BTOD REMS program:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (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 this medication is against the law

1.16 Risk Evaluation and Mitigation Strategies (REMS)

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 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
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

Medication Guide

The BTOD REMS includes product specific Medication Guides on the safe and effective use of buprenorphine-containing products, 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:

- 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

This letter is not a comprehensive description of the risks associated with the use of buprenorphine-containing transmucosal products. 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 each product covered under the BTOD REMS, can be obtained at www.btodrems.com or by contacting the toll-free call center at 1-855-223-3922.

1.16 Risk Evaluation and Mitigation Strategies (REMS)

Sincerely,

The Buprenorphine-containing Transmucosal products for Opioid Dependence Companies
Version 1.0 Revised February 2013

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

Dear Prescriber Letter

IMPORTANT DRUG WARNING

Subject: Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing transmucosal products for opioid dependence due to their 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) called the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS program. This REMS does not apply to buprenorphine-containing products that are 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 buprenorphine-containing transmucosal products for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction. Products containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. These products are used as part of a complete treatment plan, including counseling and psychosocial support.

Serious Risks of Buprenorphine-containing Products

The following key messages need to be communicated to patients about the risks of accidental overdose, misuse, and abuse while taking products covered under the BTOD REMS program:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) while taking these products. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.
- Instruct patients to keep these 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 these products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Caution patients to keep their products in a safe place, and to protect them from theft.
- Instruct patients never to give these 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 these products is against the law.

1.16 Risk Evaluation and Mitigation Strategies (REMS)

Prescriber Action

Certified prescribers must read the enclosed educational brochure entitled ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers***. Under the BTOD 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 buprenorphine-containing products, 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 BTOD 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 BTOD REMS includes product specific Medication Guides with important information to be reviewed with patients. In addition, the Medication Guide will be dispensed with each prescription for a buprenorphine-containing transmucosal product.

Reporting Adverse Events

To report SUSPECTED ADVERSE EVENTS 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

1.16 Risk Evaluation and Mitigation Strategies (REMS)

This letter is not a comprehensive description of the risks associated with the use of buprenorphine-containing transmucosal products. 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 each product covered under the BTOD REMS, can be obtained at www.btodrems.com or by contacting the toll-free call center at 1-855-223-3922.

Sincerely,

The Buprenorphine-containing Transmucosal products for Opioid Dependence Companies
Version 1.0 Revised February 2013

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 Pharmacists

Buprenorphine-Containing Transmucosal Products

I. Introduction

The purpose of this brochure is to provide pharmacists with information about the Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing products and the important safety issues and messages needed to counsel patients about its safe use. This REMS applies to buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence and buprenorphine-containing products indicated for the treatment of opioid dependence with the same types of safety concerns as the oral transmucosal products (hereinafter, “buprenorphine-containing products”). This REMS does not apply to buprenorphine-containing products that are dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

The products covered in this REMS¹ are:

- Generic equivalents of Subutex® (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv® (buprenorphine/naloxone) sublingual tablet
- Bunavail™ (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

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

¹ Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex® and buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone® are covered under the Subutex and Suboxone REMS programs.

bioavailability for each product (i.e., how much of the buprenorphine is absorbed after administration). Suboxone 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. Bunavail buccal film is available as 2.1 mg buprenorphine/0.3 mg naloxone, 4.2 mg buprenorphine/0.7 mg naloxone, and 6.3 mg buprenorphine/1 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 should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated².

Corresponding doses of buprenorphine products that contain naloxone			
Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual film	Zubsolv sublingual tablets	Bunavail buccal films
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	
	4 mg buprenorphine/ 1 mg naloxone		2.1 mg buprenorphine/ 0.3 mg naloxone
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone
	12 mg buprenorphine/ 3 mg naloxone		6.3 mg buprenorphine/ 1 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.

² 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.

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 all buprenorphine-containing products can be found at www.btodrems.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 buprenorphine-containing products?

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

These products are covered under the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS program.

The goals of the BTOD 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 BTOD REMS?

As part of the REMS, pharmacists dispensing buprenorphine-containing products for opioid dependence must supply a Medication Guide for the buprenorphine-containing product with each prescription. The Medication Guide will be provided with the product and is also available by going online to www.btodrems.com or calling 1-855-223-3922.

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. **Please refer to the Full Prescribing Information (FPI) for detailed safety-related information for buprenorphine-containing products.**

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 covered under the BTOD REMS 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

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.

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 ; DEA (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)).

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. 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 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		
Suboxone 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
Bunavail buccal films		2.1 mg buprenorphine/ 0.3 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone	6.3 mg buprenorphine/ 1 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.

For Bunavail administration, the patient should use the tongue to wet the inside of the cheek or rinse the mouth with water to moisten the area immediately before placement of Bunavail; open the Bunavail package immediately prior to use as indicated by the instructions; place the Bunavail film near the tip of a dry finger with the text facing up; place the side of the Bunavail film with the text against the inside of the cheek; press and hold the film in place for 5 seconds. Bunavail film(s) adhere to the moist buccal mucosa and should stay in place after this period. If multiple films need to be administered, the patient should immediately apply the next film. Note that when two films are required for one dose, the patient should place one film on the inside of each cheek. For doses requiring multiple films, no more than two films should be applied to the

inside of one cheek at a time. The patient should be instructed to avoid manipulating the film(s) with their tongue or finger(s) and avoid drinking or eating food until the film(s) dissolve.

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 and films (after they have been removed from the foil package) 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)
- American Society of Addiction Medicine website (www.asam.org)
- American Academy of Addiction Psychiatry website (www.aaap.org)

For more information:

www.btodrems.com

BTOD REMS call center (toll-free) 1-855-223-3922

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

Buprenorphine-Containing Transmucosal Products

I. Introduction

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) to prescribers of buprenorphine-containing oral transmucosal products who are certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This REMS applies to buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence and buprenorphine-containing products indicated for the treatment of opioid dependence with the same types of safety concerns as the oral transmucosal products (hereinafter, “buprenorphine-containing products”). This REMS does not apply to buprenorphine-containing products that are dispensed to patients admitted to an Opioid Treatment Program (OTP) under 42 CFR Part 8.

The products covered in this REMS¹ are:

- Generic equivalents of Subutex[®] (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone[®] (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv[®] (buprenorphine/naloxone) sublingual tablet
- Bunavail[™] (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

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

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.

¹ Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex[®] and buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone[®] are covered under the Subutex and Suboxone REMS programs.

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 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. Bunavail buccal film is available as 2.1 mg buprenorphine/0.3 mg naloxone, 4.2 mg buprenorphine/0.7 mg naloxone, and 6.3 mg buprenorphine/1 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 should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated².

Corresponding doses of buprenorphine products that contain naloxone			
Suboxone sublingual tablets, including generic equivalents	Suboxone sublingual film	Zubsolv sublingual tablets	Bunavail buccal films
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	
	4 mg buprenorphine/ 1 mg naloxone		2.1 mg buprenorphine/ 0.3 mg naloxone
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	4.2 mg buprenorphine/ 0.7 mg naloxone

² 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.

	12 mg buprenorphine/ 3 mg naloxone		6.3 mg buprenorphine/ 1 mg naloxone
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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 buprenorphine-containing products?

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

These products are covered under the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS program.

The goals of the BTOD 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 BTOD REMS?

To meet the requirements of the REMS and to ensure the benefits of prescribing buprenorphine-containing products 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
- Discuss the risks associated with buprenorphine-containing products, 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 BTOD REMS, prescribers of buprenorphine-containing products 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.btodrems.com or by calling 1-855-223-3922.

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. **Refer to the Full Prescribing Information (FPI) for detailed safety-related information for buprenorphine-containing products.**

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 covered under the BTOD REMS 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

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; 11.4 mg buprenorphine/2.8 mg naloxone per day for Zubsolv sublingual tablet; and 8.4 mg buprenorphine/1.4 mg naloxone per day for Bunavail buccal film. 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; 17.1 mg per day for Zubsolv; and 12.6 mg per day for Bunavail. 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 are buprenorphine-containing products supplied?

Subutex sublingual tablets, including generic equivalents	2 mg buprenorphine	8 mg buprenorphine		
Suboxone 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
Bunavail buccal film		2.1 mg buprenorphine / 0.3 mg naloxone	4.2 mg buprenorphine / 0.7 mg naloxone	6.3 mg buprenorphine / 1 mg naloxone

How should buprenorphine with or without naloxone 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.

For Bunavail administration, the patient should use the tongue to wet the inside of the cheek or rinse the mouth with water to moisten the area immediately before placement of Bunavail; open the Bunavail package immediately prior to use as indicated by the instructions; place the

Bunavail film near the tip of a dry finger with the text facing up; place the side of the Bunavail film with the text against the inside of the cheek; press and hold the film in place for 5 seconds. Bunavail film(s) adhere to the moist buccal mucosa and should stay in place after this period. If multiple films need to be administered, the patient should immediately apply the next film. Note that when two films are required for one dose, the patient should place one film on the inside of each cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time. The patient should be instructed to avoid manipulating the film(s) with their tongue or finger(s) and avoid drinking or eating food until the film(s) dissolve.

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 and films (after they have been removed from the foil package) 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.btodrems.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)
- American Academy of Addiction Psychiatry website (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.btodrems.com

BTOD REMS call center (toll-free) 1-855-223-3922

Version 3.0 Revised June 2014

1.16 Risk Evaluation and Mitigation Strategies (REMS)

BTOD Website

The BTOD Website snapshots are shown below.



Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD)

[Home](#)[Important Safety Information](#)[Medication Guides](#)[Full Prescribing Information](#)

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD)

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 BTOD 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 buprenorphine-containing transmucosal products indicated for the 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 products covered under the BTOD REMS, a prescriber must be certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). For certification information, [click here](#).

[Click here for a complete list of products covered under the BTOD REMS program](#)

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: **1-855-223-3922**.

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

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1.16 Risk Evaluation and Mitigation Strategies (REMS)



Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD)

[Home](#)[Important Safety Information](#)[Medication Guides](#)[Full Prescribing Information](#)

Important Safety Information

The drug products subject to the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS¹ include:

- Generic equivalents of Subutex® (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv® (buprenorphine/naloxone) sublingual tablet

¹Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex® and buprenorphine hydrochloride/naloxone hydrochloride sublingual tablets and sublingual film marketed under the trade name Suboxone® are covered under the Subutex and Suboxone REMS programs.

These products, collectively referred to as "buprenorphine-containing products", are delivered by the oral transmucosal route and are indicated for use during 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 [Full Prescribing Information](#) of each specific product for a complete list.

For more information about the BTOD REMS, including all program materials and instructions call 1-855-223-3922.

To report SUSPECTED ADVERSE EVENTS, 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

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: 1-855-223-3922.

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

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1.16 Risk Evaluation and Mitigation Strategies (REMS)



Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD)

[Home](#)[Important Safety Information](#)[Medication Guides](#)[Full Prescribing Information](#)

Buprenorphine Single Ingredient Products			
Trade Name	Company	Phone Number	Information Links

Buprenorphine/Naloxone Combination Ingredient Products			
Trade Name	Company	Phone Number	Information Links

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: **1-855-223-3922**.

The BPMG attests that the table above will only include products listed in the link titled 'List of approved application numbers and sponsors' on the FDA Approved REMS website.

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

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1.16 Risk Evaluation and Mitigation Strategies (REMS)



Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD)

[Home](#)[Important Safety Information](#)[Medication Guides](#)[Full Prescribing Information](#)

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, or by contacting SAMHSA directly:

SAMHSA Buprenorphine Information Center
Phone: 1-866-287-2729 (866-BUP-CSAT)
E-mail: info@buprenorphine.samhsa.gov

Materials for Prescribers:

[Dear Prescriber Letter](#)

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

[Appropriate Use Checklist](#)

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[Dear Pharmacist Letter](#)

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Proposed changes to the website include additions to the Important Safety Information as shown in tracked changes below to include Bunavail and the most common adverse reactions with Bunavail buccal film as described in the PI Highlights adverse reaction section:

Important Safety Information

The drug products subject to the Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS¹ include:

- Generic equivalents of Subutex[®] (buprenorphine hydrochloride) sublingual tablet
- Generic equivalents of Suboxone[®] (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- Zubsolv[®] (buprenorphine/naloxone) sublingual tablet
- Bunavail[™] (buprenorphine hydrochloride/naloxone hydrochloride) buccal film

1.16 Risk Evaluation and Mitigation Strategies (REMS)

¹Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex[®] and buprenorphine hydrochloride/naloxone hydrochloride sublingual film marketed under the trade name Suboxone[®] is covered under the Suboxone REMS program.

These products, collectively referred to as “buprenorphine-containing products”, are delivered by the oral transmucosal route and are indicated for use during 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.

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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.

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1.16 Risk Evaluation and Mitigation Strategies (REMS)

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 Full Prescribing Information of each specific product for a complete list.

For more information about the BTOD REMS, including all program materials and instructions call **1-855-223-3922**.

To report SUSPECTED ADVERSE EVENTS, 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

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

/s/

JAMIE C WILKINS PARKER
06/05/2014

CLAUDIA B MANZO
06/05/2014
concur