Initial REMS approval: 08/2010
Most recent modification: 07/2016

NDA 22-410
SUBOXONE® (buprenorphine and naloxone) Sublingual Film CIII
NDA 20-733
SUBOXONE® (buprenorphine and naloxone) Sublingual Tablets CIII
NDA 20-732
SUBUTEX® (buprenorphine) Sublingual Tablets CIII
Buprenorphine (opioid partial agonist-antagonist)
Naloxone (opioid antagonist)

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

This REMS does not apply to SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets dispensed to patients admitted to an Opioid Treatment Program (OTP) under 42 CFR Part 8 because the care of OTP patients is subject to specific requirements under those regulations.

I. GOAL(S):

The goals of the REMS for SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets are to:

- Mitigate the risks of accidental overdose, misuse and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets

Reference ID: 3956127

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets prescription in accordance with 21 CFR 208.24.

The Medication Guides for buprenorphine-containing products are part of the SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets REMS and will be provided with the product and is also available by going online to www.suboxoneREMS.com or calling 1-866-463-4846.

B. Elements to Assure Safe Use

1. Safe use conditions

a. SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets 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. Indivior Inc. will ensure that within 30 days of FDA approval of the SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets REMS, a Dear Prescriber Letter will be mailed to all physicians 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 SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets, 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 Guide. Mailings will occur annually thereafter.

d. Indivior Inc. will, on a monthly basis, identify any newly DATA 2000-certified physicians and mail the applicable documents to them. The prescriber brochure, *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers* will be appended to the Dear Prescriber Letter as well as the Medication Guide, Full Prescribing Information, and the Appropriate Use Checklist.
e. To further reinforce safe use conditions, Indivior Inc. will ensure that within 30 days of FDA approval of the SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets REMS, a Dear Pharmacist Letter will be mailed to all pharmacists on a national mailing list of all retail pharmacies authorized by DEA to handle schedule 3 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 as well as the Medication Guide, and Full Prescribing Information. Mailings will occur annually thereafter.
f. Indivior Inc. will make the letters and all materials that are appended to the letters available through its toll-free information line, through its field personnel, and on the SUBOXONE and SUBUTEX REMS website.

2. Monitoring

a. Each patient using SUBOXONE sublingual film, SUBOXONE sublingual tablets and SUBUTEX sublingual tablets 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 REMS and are appended to the REMS document:

- SUBOXONE sublingual film Medication Guide
- SUBOXONE sublingual tablets Medication Guide
- SUBUTEX sublingual tablets Medication Guide
- 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"*
- SUBOXONE and SUBUTEX REMS website (www.suboxoneREMS.com)

C. Implementation System

The Implementation System includes the following:

1. Indivior Inc. will ensure that all DATA 2000-certified physicians receive the Dear Prescriber Letter with the appended materials.
2. Indivior Inc. will monitor compliance with the 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, street ethnography, national databases, and surveys conducted at substance abuse treatment programs).
3. Indivior Inc. will monitor and evaluate the implementation of the elements to assure safe use provided for under Sections B1, above, and in the manner described in the REMS supporting document, and will take reasonable steps to improve implementation of these elements to meet the goals of the REMS.

D. Timetable for Submission of Assessments

Indivior Inc. will submit REMS Assessments to FDA at 6 months and at 12 months for the first year from the date of approval of the REMS, then annually thereafter. 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. Indivior Inc. will submit each assessment so it will be received by the FDA on or before the due date.

INDIVIOR

SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets

Risk Evaluation and Mitigation Strategy (REMS) Program

Office-Based Buprenorphine Therapy for Opioid Dependence:

Important Information for Prescribers

SUBOXONE®
(buprenorphine and naloxone)
sublingual film CIII

SUBOXONE®
(buprenorphine and naloxone)
sublingual tablets CIII

SUBUTEX®
(buprenorphine)
sublingual tablets CIII

Reference ID: 3956127

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I. SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets REMS

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) Program 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 brochure summarizes selected important safety issues and messages needed to manage and counsel patients about safe use of these products. For additional safety information, be sure to read the prescribing information.

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

A REMS is a strategy to mitigate a known or potential serious risk associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.

Why is there a REMS for buprenorphine-containing products?

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.

Buprenorphine, like morphine and other opioids, has the potential for being abused and misused. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant use of buprenorphine and alcohol or other central nervous system (CNS) depressants, especially benzodiazepines.

As part of this REMS, manufacturers of buprenorphine products have worked with the FDA to educate prescribers, pharmacists, and patients about the serious risks associated with the use of buprenorphine-containing products.

This REMS applies to:

- buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence

Note: 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 following products are covered under the SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets REMS Program:

- SUBOXONE® (buprenorphine/naloxone) sublingual film
- SUBOXONE® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- SUBUTEX® (buprenorphine hydrochloride) sublingual tablet

The goals of the 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 actions should I take as a prescriber to comply with the 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 appropriate diagnostic criteria.
- **Discuss the risks** (including misuse and abuse) **and side effects** associated with buprenorphine-containing products, including those described in the Medication Guide (See Section III for important safety information regarding these risks.).
- Explain what patients should do if they experience side effects.
- 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/film count"/dose reconciliation.
- Assess whether patient is receiving counseling/psychosocial support considered necessary for treatment **and if not, encourage them to do so** (See Section VI).
- Assess whether patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing).
- Continually assess appropriateness of maintenance dose (See Section IV).
- Continually assess whether or not benefits of treatment outweigh the risks.

How should I monitor patients and ensure appropriate dosing of buprenorphine products?

As part of the 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.suboxonerems.com or by calling Indivior Inc. at 1-866-463-4846.

What information about the safe use of buprenorphine-containing products needs to be communicated to patients?

The following key messages need to be communicated to patients about safe use of products covered under the REMS to mitigate **the serious risks of accidental overdose, misuse, and abuse**:

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.

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 never to give these products to anyone else, even if he or she has the same signs and symptoms. They may cause harm or death.

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 and secure place, out of the reach of children, and to protect them from theft.

Advise patients that selling or giving away these products is against the law.

Use the contents of each drug product's Medication Guide, in its entirety, with each patient to review the information noted above, including side effects and what to do if a patient has them. The Medication Guide will be dispensed with each prescription for a buprenorphine-containing transmucosal product.

Strongly encourage patients to seek psychosocial counseling and support for safe and effective treatment.

II. Buprenorphine Product Information Relevant to the REMS Goals

What are buprenorphine-containing products and their uses?

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with naloxone; both types of products are indicated for the treatment of opioid dependence.

The second active ingredient in some products, naloxone HCl, is intended to deter abuse by the intravenous route of buprenorphine-containing products by people who are dependent on full opioid agonists.

Specific Uses for Formulations of Buprenorphine-containing Products:

Buprenorphine-only products are preferred for initiating treatment (**induction**) in patients physically dependent on methadone or long-acting opioids. SUBOXONE Sublingual Film is one of several buprenorphine/naloxone containing-products that may be used for **induction** in patients physically dependent on heroin or other short-acting opioids. All products can be used for **maintenance**.

However, in patients with severe hepatic impairment and in pregnant patients, buprenorphine-only products should be used for both **induction** and **maintenance**.

Buprenorphine-containing products are used as only one part of a complete treatment plan that includes 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, site of administration, 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).

What are the corresponding doses of buprenorphine products that contain naloxone?

Patients being switched between different formulations should be started on the corresponding dose (as shown in Table 1 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 indicated.[1]

Table 1
Corresponding Doses of Buprenorphine-Containing Products

Product Name	Buprenorphine sublingual tablets (SUBUTEX)	Buprenorphine/ Naloxone sublingual tablets (SUBOXONE)	Buprenorphine/ Naloxone sublingual films (SUBOXONE)	Buprenorphine/ Naloxone sublingual tablets (Zubsolv)	Buprenorphine/ Naloxone buccal films (Bunavail)
	2 mg buprenorphine	2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	1 mg buprenorphine/ 0.2 mg naloxone
	8 mg buprenorphine		4 mg buprenorphine/ 1 mg naloxone	2.9 mg buprenorphine/ 0.71 mg naloxone	2.1 mg buprenorphine/ 0.3 mg naloxone
Dose Strengths Available		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	8.6 mg buprenorphine/ 2.1 mg naloxone	6.3 mg buprenorphine/ 1 mg naloxone
				11.4 mg buprenorphine/ 2.9 mg naloxone	
Route of Administration	Sublingual	Sublingual	Sublingual Buccal	Sublingual	Buccal

[1] Note that, although the nominal SUBOXONE film doses are the same as the SUBOXONE tablets and generic equivalent tablets, not all strengths and combinations of the films are bioequivalent to the generic equivalent or Zubsolv tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

III. Highlighted Important Safety Information for Buprenorphine-Containing Products

This section of the brochure highlights some of the important safety information to consider when prescribing buprenorphine-containing products. **Refer to the Prescribing Information (PI) for detailed safety-related information for each of the buprenorphine-containing products.**

- **Store buprenorphine-containing products safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children**.
- 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, as patients may exhibit increased CNS depression.
- **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.
- 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 this REMS are not appropriate as analgesics. 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 while taking buprenorphine-containing products.
- 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

IV. Prescribing Buprenorphine-Containing Products

INDUCTION WITH BUPRENORPHINE-CONTAINING PRODUCTS

What is the proper protocol for induction?

Prior to induction, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence.

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.

What dosages should be used to initiate treatment with buprenorphine-containing products?

On Day 1, a total induction dosage of the equivalent of 8 mg of buprenorphine in SUBUTEX or SUBOXONE (see table 1 for corresponding doses) is recommended. Clinicians should start with an initial dose of 2 mg or 4 mg of buprenorphine in SUBUTEX or SUBOXONE or equivalent and may titrate upwards in 2 mg or 4 mg increments (at approximately 2-hour intervals, under supervision) to 8 mg total based on the control of acute withdrawal signs. On Day 2, a single dose of up to 16 mg buprenorphine in SUBUTEX or SUBOXONE or equivalent is recommended.

Because the exposure to naloxone in naloxone-containing products is somewhat higher after buccal administration than after sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimize exposure to naloxone, to reduce the risk of precipitated withdrawal.

MAINTENANCE WITH BUPRENORPHINE-CONTAINING PRODUCTS

How do I maintain clinically effective dosing for stabilized patients?

The recommended target dose is 16 mg buprenorphine/4 mg naloxone per day for Suboxone sublingual tablets and sublingual film, including generic equivalents, and is 11.4 mg buprenorphine/2.8 mg naloxone per day for Zubsolv sublingual tablet, 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 tablets and 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 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 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.

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

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, taper the dose, rather than abruptly discontinuing. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

V. Preventing Diversion and Abuse

It is critical to prevent diversion and abuse of buprenorphine-containing products in order to mitigate the risks of accidental overdose, misuse, and abuse.

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 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.
- Check the applicable state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
- 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.
- 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.

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. 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.

VI. 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, and **patients should be strongly encouraged to obtain such support and counseling for safe and effective treatment**. 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.

VII. Additional Information on Treating Opioid Addiction with Buprenorphine-Containing Products

Refer to the package insert for Prescribing Information, which can be found at www.suboxonerems.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://pcssmat.org)

For more information:

Call Indivior Inc. at 1-866-463-4846 or visit www.suboxonerems.com

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Richmond, VA 23235

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Reference ID: 3956127

INDIVIOR

SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets

Risk Evaluation and Mitigation Strategy (REMS) Program

Office-Based Buprenorphine Therapy for Opioid Dependence:

Important Information for Pharmacists

SUBOXONE®
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I. SUBOXONE Sublingual Film, SUBOXONE Sublingual Tablets, and SUBUTEX Sublingual Tablets REMS

The purpose of this brochure is to provide pharmacists with information about the Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing products. This brochure summarizes selected important safety issues and messages needed to manage and counsel patients about safe use of these products. For additional safety information, be sure to read the prescribing information.

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

A REMS is a strategy to mitigate a known or potential serious risk associated with a drug and is required by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks.

Why is there a REMS for buprenorphine-containing products?

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.

Buprenorphine, like morphine and other opioids, has the potential for being abused and misused. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant use of buprenorphine and alcohol and other central nervous system (CNS) depressants, especially benzodiazepines.

As part of this REMS, manufacturers of buprenorphine products have worked with the FDA to educate prescribers, pharmacists, and patients about the serious risks associated with the use of buprenorphine-containing products.

This REMS applies to:

> buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence

Note: 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 following products are covered under the SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX REMS Program:

> SUBOXONE® (buprenorphine/naloxone) sublingual film

> SUBOXONE® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet

> SUBUTEX® (buprenorphine hydrochloride) sublingual tablet

What action should I take as a pharmacist to comply with this 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.suboxonerems.com or calling Indivior Inc. at 1-866-463-4846.

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 the Drug Addiction Treatment Act of 2000 (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 for prescribers to closely and frequently assess the patients' needs, their symptoms, and potential risk of misuse, diversion, and abuse.

> Pharmacists should also check state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.

> **Provide the Medication Guide to patients** each time the medicine is dispensed and discuss the risks and side effects associated with buprenorphine products, including what to do if patients experience side effects.

> 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.

> Explain how to safely store the medication out of reach of children, provide appropriate patient counseling on safe use of buprenorphine-containing products and **encourage patients to seek psychosocial counseling and support for safe and effective treatment**.

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

What information about the safe use of buprenorphine-containing products needs to be communicated to patients?

The following key messages need to be communicated to patients about safe use of products covered under the REMS to mitigate **the serious risks of accidental overdose, misuse, and abuse:**

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.

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 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 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 secure and safe place, out of the reach of children, and to protect them from theft.

Advise patients that selling or giving away these products is against the law.

Use the contents of each drug product's Medication Guide, in its entirety, with each patient to review the information noted above including side effects and what to do if a patient has them. The Medication Guide will be dispensed with each prescription for a buprenorphine-containing transmucosal product.

Strongly encourage patients to seek psychosocial counseling and support for safe and effective treatment.

II. Buprenorphine Product Information Relevant to the REMS Goals

What are buprenorphine-containing products and their uses?

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with naloxone; both types of products are indicated for the treatment of opioid dependence.

The second active ingredient in some products, naloxone HCl, is intended to deter abuse by the intravenous route of buprenorphine-containing products by people who are dependent on full opioid agonists. Prescribers are instructed to limit the use of buprenorphine-only products, such as buprenorphine sublingual tablets, to supervised use, wherever possible.

Specific Uses for Formulations of Buprenorphine-containing Products:

Buprenorphine-only products are preferred for initiating treatment (**induction**) in patients physically dependent on methadone or long-acting opioids. SUBOXONE Sublingual Film is one of several buprenorphine/naloxone containing-products that may be used for **induction** in patients physically dependent on heroin or other short-acting opioids. All products can be used for **maintenance**.

However, in patients with severe hepatic impairment and in pregnant patients, buprenorphine-only products should be used for both **induction** and **maintenance**.

Buprenorphine-containing products are used as only one 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, site of administration, 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).

What are the corresponding doses of buprenorphine products that contain naloxone?

Patients being switched between different formulations should be started on the corresponding dose (as shown in Table 1 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 indicated.[1]

Table 1
Corresponding doses of buprenorphine products that contain naloxone

Product Name	Buprenorphine sublingual tablets, (SUBUTEX)	Buprenorphine/ Naloxone sublingual tablets, (SUBOXONE)	Buprenorphine/ Naloxone sublingual films (SUBOXONE)	Buprenorphine/ Naloxone sublingual tablets (Zubsolv)	Buprenorphine/ Naloxone buccal films (Bunavail)
	2 mg buprenorphine	2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone	1 mg buprenorphine/ 0.2 mg naloxone
			4 mg buprenorphine/ 1 mg naloxone	2.9 mg buprenorphine/ 0.71 mg naloxone	2.1 mg buprenorphine/ 0.3 mg naloxone
Dose Strengths Available	8 mg buprenorphine	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	8.6 mg buprenorphine/ 2.1 mg naloxone	6.3 mg buprenorphine/ 1 mg naloxone
				11.4 mg buprenorphine/ 2.9 mg naloxone	
Route of Administration	Sublingual	Sublingual	Sublingual Buccal	Sublingual	Buccal

[1] Note that, although the nominal SUBOXONE Film doses are the same as the SUBOXONE Tablet and generic equivalent tablets, not all strengths and combinations of the films are bioequivalent to the generic equivalent or Zubsolv tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

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 Prescribing Information (PI) for detailed safety-related information for buprenorphine-containing products.**

- **Store buprenorphine-containing products safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children.**
- 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, as patients may exhibit increased CNS depression.
- **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.
- 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 this REMS are not appropriate as analgesics. 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 while taking buprenorphine-containing products.
- 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

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. These prescribers will have a special DEA number starting with the letter "X". 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.

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 1-866-BUP-CSAT (1-866-287-2728), or e-mailing *info@buprenorphine.samhsa.gov*.

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 two or more qualified prescribers and therefore, receive multiple prescriptions for buprenorphine-containing products. If a patient brings you more than one 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. The federal requirements discussed above regarding obtaining signed consent and redisclosure do not apply when it is the patient who delivers the prescription to the pharmacist, without direct communication from the prescriber to the pharmacist.

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. Where can I get more information on treating opioid dependence 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:

Call Indivior Inc. at 1-866-463-4846 or visit www.suboxonerems.com

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Richmond, VA 23235

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July 2016

Reference ID: 3956127

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FPO

<Address Area>

IMPORTANT DRUG WARNING

Subject: Risk Evaluation and Mitigation Strategy (REMS) for
SUBOXONE® (buprenorphine and naloxone) Sublingual Film CIII
SUBOXONE® (buprenorphine and naloxone) Sublingual Tablets CIII
SUBUTEX® (buprenorphine) Sublingual Tablets CIII

<DATE>

Dear Prescriber:

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

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE sublingual film, SUBOXONE sublingual tablets, SUBUTEX sublingual tablets, and the generic equivalent products, hereafter collectively called buprenorphine-containing products. 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 products for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Buprenorphine, like morphine and other opioids, has the potential for being abused and misused. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant use of buprenorphine and alcohol and other central nervous system (CNS) depressants, especially benzodiazepines.

SUBUTEX sublingual tablets, SUBOXONE sublingual tablets, and SUBOXONE sublingual film are partial-opioid agonists indicated for the treatment of opioid dependence. Products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction. SUBOXONE sublingual film is one of several buprenorphine/naloxone-containing products that may be used for **induction** in patients physically dependent on heroin or other short-acting opioids. All products can be used for **maintenance**.

Prescriber Action

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:

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- Verify the patient meets appropriate diagnostic criteria for opioid dependence
- **Discuss the risks** (including misuse and abuse) **and side effects** associated with buprenorphine-containing products, including those described in the Medication Guide
- Explain what patients should do if they experience side effects
- 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/film count"/dose reconciliation
- Assess whether the patient is receiving the counseling/psychosocial support considered necessary for treatment, **and if not, encourage them to do so**
- Assess whether the 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

Serious Risks of Buprenorphine-containing Products

The following key messages need to be communicated to patients about safe use of products covered under the REMS to mitigate **the serious risks of accidental overdose, misuse, and abuse**:

- **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.**
- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) with these products. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.
- Instruct patients never to give these products to anyone else, even if he or she has the same signs and symptoms. They may cause harm or death.
- Advise patients that buprenorphine-containing 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 and secure place, out of the reach of children, and to protect them from theft.
- Advise patients that selling or giving away buprenorphine-containing products is against the law.
- **Use the contents of each buprenorphine-containing drug product's Medication Guide**, in its entirety, with each patient to review the information noted above, including side effects and what to do if a patient has them. The Medication Guide will be dispensed with each prescription for a buprenorphine-containing transmucosal product.
- **Strongly encourage patients to seek psychosocial counseling and support for safe and effective treatment.**

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 SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets 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.

Reporting Adverse Events

To report SUSPECTED ADVERSE EVENTS contact:

- Indivior Inc. at 1-877-782-6966 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 products. Additional important safety information can be found in the ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers*** educational brochure and Prescribing Information.

Additional copies of the educational brochure, Appropriate Use Checklist, Prescribing Information, and Medication Guide for each product covered under the SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets REMS, can be obtained at www.suboxonerems.com, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm or by contacting the toll-free call center at 1-866-463-4846.

Sincerely,

<NAME>
<TITLE>

Indivior Inc.

Enclosures:
Appropriate Use Checklist
Prescriber Brochure: *"Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers"*

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<Address Area>

IMPORTANT DRUG WARNING

Subject: Risk Evaluation and Mitigation Strategy (REMS) for
SUBOXONE® (buprenorphine and naloxone) Sublingual Film CIII
SUBOXONE® (buprenorphine and naloxone) Sublingual Tablets CIII
SUBUTEX® (buprenorphine) Sublingual Tablets CIII

<DATE>

Dear Pharmacist:

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE sublingual film, SUBOXONE sublingual tablets, SUBUTEX sublingual tablets, and the generic equivalent products, hereafter collectively called buprenorphine-containing products. 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.

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SUBUTEX sublingual tablets, SUBOXONE sublingual tablets, and SUBOXONE sublingual film are partial-opioid agonists indicated for the treatment of opioid dependence. Products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction. SUBOXONE sublingual film is one of several buprenorphine/naloxone-containing products that may be used for **induction** in patients physically dependent on heroin or other short-acting opioids. All products can be used for **maintenance**.

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

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Pharmacist Action

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 and discuss the risks and side effects associated with buprenorphine products, including what to do if patients experience side effects.
- 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.
- Explain how to safely store the medication out of reach of children.
- Provide appropriate patient counseling on the safe use of buprenorphine-containing products and **encourage patients to seek psychosocial counseling and support for safe and effective treatment**.
- Pharmacists should also check state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse. Pharmacists should be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers.

Serious Risks of Buprenorphine-containing Products

The following key messages need to be communicated to patients about safe use of products covered under the REMS to mitigate **the serious risks of accidental overdose, misuse and abuse**:

- **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 and secure place, out of the reach of children, and to protect them from theft.
- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) with these products. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.
- Advise patients that selling or giving away these products is against the law.

- **Use the contents of each drug product's Medication Guide**, in its entirety, with each patient to review the information noted above including side effects and what to do if a patient has them. The Medication Guide will be dispensed with each prescription for a buprenorphine-containing transmucosal product.
- **Strongly encourage patients to seek psychosocial counselling and support for safe and effective treatment.**

Medication Guide

- 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.suboxonerems.com or by calling 1-866-463-4846.

Reporting Adverse Events

To report SUSPECTED ADVERSE EVENTS contact:

- Indivior Inc. at 1-877-782-6966 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 products. Additional important safety information can be found in the ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*** educational brochure and the Prescribing Information.

Additional copies of the educational brochure, Prescribing Information, and Medication Guide for each product covered under the SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets REMS, can be obtained at www.suboxonerems.com, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm or by contacting the toll-free call center at 1-866-463-4846.

Sincerely,

<NAME>
<TITLE>

Indivior Inc.

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

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SUBOXONE® SUBLINGUAL FILM, SUBOXONE® SUBLINGUAL TABLET, AND SUBUTEX® SUBLINGUAL TABLET APPROPRIATE USE CHECKLIST:

This checklist is a useful reminder of the safe use conditions and monitoring requirements for prescribing SUBOXONE (buprenorphine and naloxone) sublingual film CIII, SUBOXONE (buprenorphine and naloxone) sublingual tablets CIII, or SUBUTEX (buprenorphine) sublingual tablets CIII 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: www.pcssmat.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 appropriate 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, including keeping it out of the sight and reach of children	
○ 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	

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SUBOXONE® SUBLINGUAL FILM, SUBOXONE® SUBLINGUAL TABLET, AND SUBUTEX® SUBLINGUAL TABLET APPROPRIATE USE CHECKLIST:

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/film count/dose reconciliation	
◯ Assessed appropriateness of dosage > Buprenorphine combined with naloxone is recommended for maintenance: —Buprenorphine/Naloxone (SUBOXONE) sublingual film and (SUBOXONE) sublingual tablets: 16 mg/4 mg is the recommended dose for maintenance —Buprenorphine/Naloxone (Zubsolv®) sublingual tablets: a target dose of 11.4 mg buprenorphine is recommended for maintenance —Buprenorphine/Naloxone (Bunavail®) buccal film: a target dose of 8.4 mg of buprenorphine is recommended for maintenance —Buprenorphine (SUBUTEX) sublingual tablets and generic formulations may be appropriate for maintenance for some patients (e.g., pregnancy, liver disease): 4 mg to 24 mg is the recommended dose range 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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ZUBSOLV® is a registered trademark of Orexo US, Inc.
BUNAVAIL® is a registered trademark owned by BioDelivery Sciences International, Inc.

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Reference ID: 3956127

SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII)
SUBOXONE® (buprenorphine and naloxone) Sublingual Tablet (CIII)
SUBUTEX® (buprenorphine) Tablet (CIII)

Risk Evaluation and Mitigation Strategy (REMS)

What is the SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets REMS?

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets. A REMS is a strategy to mitigate 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 SUBOXONE Film, SUBOXONE Tablet, and SUBUTEX Tablet 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.

What products are covered under the SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets REMS?

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with naloxone; both types of products are indicated for the treatment of opioid dependence.

The following products are covered under the SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets REMS Program:

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- SUBOXONE® (buprenorphine hydrochloride/naloxone hydrochloride) sublingual tablet
- SUBUTEX® (buprenorphine hydrochloride) sublingual tablet

The use of buprenorphine-containing products should be 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.

Where can I obtain additional information?

Please see the Prescribing Information and Medication Guides for all three buprenorphine-containing products.

For more information about the SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets REMS, including all program materials and instructions call 1-866-463-4846 or visit www.SuboxoneREMS.com

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*)

To report SUSPECTED ADVERSE EVENTS, contact:

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- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

Materials for Prescribers:

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

Materials for Pharmacists:

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

Materials for Patients:

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SUBOXONE Tablet Med Guide
SUBUTEX Med Guide

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Where can I obtain additional information?

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Prescribers

Prescribers play an important role in reducing the risks of accidental overdose, misuse, and abuse, associated with buprenorphine-containing transmucosal products. To help mitigate these risks, prescribers should:

- **Verify** the patient meets appropriate diagnostic criteria.
- **Discuss the risks** (including misuse and abuse) **and side effects** associated with buprenorphine-containing products, including those described in the Medication Guide. (See the brochure, ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers*** for additional safety information regarding these risks.)
- **Explain** what patients should do if they experience side effects.
- **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 the reach of children.
- **Schedule** patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month).
- **Consider** "pill/film count"/dose reconciliation.
- **Assess**:
  - whether patient is receiving counseling/psychosocial support considered necessary for treatment and if not, encourage them to do so.
  - whether patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing).
  - the appropriateness of the maintenance dose.
  - whether or not benefits of treatment outweigh the risks.

To prescribe products covered under the SUBOXONE Film, SUBOXONE Tablets, and SUBUTEX Tablets 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.

Materials for Prescribers:

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Pharmacists

Pharmacists play an important role in reducing the risks of accidental overdose, misuse, and abuse, associated with buprenorphine-containing transmucosal products. To help mitigate these risks, pharmacists should:

- **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.
- **Check** state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
- **Provide** the Medication Guide to patients each time the medicine is dispensed and discuss the risks and side effects associated with buprenorphine products, including what to do if patients experience side effects.
- **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.
- **Explain** how to safely store the medication out of the reach of children.
- **Provide** appropriate patient counseling on safe use of buprenorphine-containing products and encourage patients to seek psychosocial counseling and support for safe and effective treatment. Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers.
- **Review** the brochure ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*** for additional information.

Materials for Prescribers:

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Materials for Pharmacists:

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Educating Patients

The SUBOXONE Film, SUBOXONE Tablet, and SUBUTEX Tablet Medication Guides are a core component of the REMS program. Each respective Medication Guide contains important information about the product, including proper administration, potential adverse events, and other precautions.

You should review the medication guide with patients for whom you prescribe SUBOXONE Film, SUBOXONE Tablet, or SUBUTEX Tablet to ensure that they understand the proper use and safety precautions associated with these products. You have received a tear pad with medication guides that you can distribute to patients. If you require additional copies of the medication guide, you can request them through your Clinical Liaison or by calling 1-866-463-4846.

Additionally, tear pads of the medication guides are provided to pharmacies that order and dispense SUBOXONE Film, SUBOXONE Tablet or SUBUTEX Tablet with reminders that they should provide the correct Medication Guide with every prescription.

Communicate the following **messages** to patients about the **risks of accidental overdose, misuse, and abuse**:

- 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 never to give these products to anyone else, even if he or she has the same signs and symptoms. They may cause harm or death.
- 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 and secure place, out of the reach of children, and to protect them from theft.
- Advise patients that selling or giving away these products is against the law.
- **Strongly encourage patients to seek psychosocial counseling and support for safe and effective treatment.**

Additional information about safe use conditions and patient monitoring can be found in the Prescriber Brochure and in the warning and precautions sections of the product-specific Prescribing Information.

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Where can I obtain additional information?

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

/s/

JUDITH A RACOOSIN
07/07/2016