



BTOD|REMS

BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS
FOR THE TREATMENT OF OPIOID DEPENDENCE (BTOD)

RISK EVALUATION AND MITIGATION STRATEGY
(REMS) PROGRAM

OFFICE-BASED BUPRENORPHINE
THERAPY FOR OPIOID DEPENDENCE:

IMPORTANT INFORMATION FOR PRESCRIBERS

TABLE OF CONTENTS

Section I. BTOD REMS	p. 2
Section II. Buprenorphine Product Information Relevant to the REMS Goals.....	p. 3
Section III. Highlighted Important Safety Information for Buprenorphine-containing Products	p. 4
Section IV. Prescribing Buprenorphine-containing Products.....	p. 4
Section V. Preventing Diversion and Abuse.....	p. 6
Section VI. Psychosocial Support and Other Patient Counseling.....	p. 6
Section VII. Additional Information on Treating Opioid Addiction.....	p. 6
with Buprenorphine-containing Products	

I. BTOD REMS

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 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 manage 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 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 Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS Program:

- Generic equivalents of Subutex® (buprenorphine) sublingual tablets
- Generic equivalents of Suboxone® (buprenorphine and naloxone) sublingual tablets and sublingual films
- Zubsolv® (buprenorphine and naloxone) sublingual tablets
- Bunavail® (buprenorphine and naloxone) buccal films
- Cassipa® (buprenorphine and naloxone) sublingual films

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 action should I take as a prescriber to comply with 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 appropriate diagnostic criteria.
- Check patient's prescription profile in the Prescription Drug Monitoring Program, as appropriate, and review all medications (e.g., benzodiazepines, other opioids, CNS depressants) and illicit substances to assess for appropriateness of co-prescribing.
- **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 store the medication safely out of sight and reach of all others, especially 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 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.

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:**

- **Instruct patients to keep these products in a secure place, out of the sight and reach of all others, especially children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Advise patients to seek medical attention immediately if a child is exposed to one of these products.**
- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other 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.
- Advise patients to never 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 secure and safe place, out of the sight and reach of all others, especially 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 BTOD 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 buprenorphine only 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. Products that contain buprenorphine with naloxone 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, buprenorphine-only products should be used for both **induction** and **maintenance**. Because of a lack of information about the safety of naloxone in pregnancy, buprenorphine-only products are also recommended for pregnant patients.

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 indicated¹.

¹ 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 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.

		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®)	Buprenorphine/Naloxone sublingual films (Cassipa®)
Dose Strengths Available				0.7 mg buprenorphine/ 0.18 mg naloxone		
	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		
			4 mg buprenorphine/ 1 mg naloxone	2.9 mg buprenorphine/ 0.71 mg naloxone	2.1 mg buprenorphine/ 0.3 mg naloxone	
	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		16 mg buprenorphine/ 4 mg naloxone	
Route of Administration	Sublingual	Sublingual	Sublingual Buccal	Sublingual	Buccal	Sublingual

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 all others, especially children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children.**
- Life-threatening respiratory depression and death have occurred in association with buprenorphine use. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants (including alcohol) while under treatment with buprenorphine-containing products.
- **Buprenorphine can be abused in a similar manner to other opioids.** Clinical monitoring appropriate to the patient's level of stability is essential. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits.
- If treatment is temporarily interrupted or discontinued, monitor patients for withdrawal and treat appropriately.

- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events.
- Buprenorphine or naloxone-containing products are contraindicated in patients with a history of hypersensitivity to buprenorphine or naloxone.
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of buprenorphine-containing products by individuals physically dependent on full opioid agonists, or by sublingual or buccal administration before the agonist effects of other opioids have subsided, particularly in buprenorphine-containing products that also contain naloxone.
- Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy.
- Buprenorphine-containing products covered under the BTOD 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, a too-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 treatment 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
 - Cassipa sublingual film
- 11.4 mg buprenorphine/2.9 mg naloxone per day for Zubsolv sublingual tablet
- 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, 17.2 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 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, www.samhsa.gov, or call 1-866-BUP-CSAT (1-866-287-2728).

What can I tell patients who wish to discontinue treatment?

Advise patients not to change the dosage of buprenorphine-containing products without consulting their prescriber. Advise patients seeking to discontinue treatment with buprenorphine-containing products for opioid dependence to work closely with their prescriber on a tapering schedule and inform them 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, gradually 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 opioid 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.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 (SAMHSA). Additional information is also available on the SAMHSA website at www.samhsa.gov.

General information about buprenorphine treatment and treatment of addiction is 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)
- Providers Clinical Support System for Medication Assisted Treatment (pcssnow.org)

For more information:

www.btodrems.com

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