BTOD|REMS

Buprenorphine-Containing Transmucosal Products for the Treatment of Opioid Dependence (BTOD)

Risk **E**valuation and **M**itigation **S**trategy (REMS)[1]

Important Drug Safety Information for Prescribers

[1] Note: This REMS does **not** apply to buprenorphine-containing products that are dispensed to patients undergoing treatment through an Opioid Treatment Program (OTP) under 42 CFR Part 8.

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I. BTOD REMS

The purpose of this brochure is to provide information about the **R**isk **E**valuation and **M**itigation **S**trategy (REMS) to prescribers of buprenorphine-containing transmucosal products for opioid dependence (BTODs). This brochure highlights selected important safety issues and messages needed to manage and counsel patients about safe use of these products. For complete 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 BTODs?

A REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with BTODs outweigh the potential risks.

Buprenorphine is an opioid and, like 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 BTODs.

This REMS applies to:

- BTODs indicated for the treatment of opioid dependence

Note: This REMS does **not** apply to buprenorphine-containing products that are dispensed to patients undergoing treatment through an Opioid Treatment Program (OTP) under 42 CFR Part 8.

The following products are covered under the BTOD REMS:

- Generic equivalents of Subutex® (buprenorphine) sublingual tablets
- Generic equivalents of Suboxone® (buprenorphine and naloxone) sublingual tablets
- Suboxone® (buprenorphine and naloxone) sublingual films and generic equivalents
- Zubsolv® (buprenorphine and naloxone) sublingual tablets
- 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 BTODs

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 BTODs 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 the 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 BTODs, including those described in the Medication Guide. (See Section III for important safety information regarding these risks.)
- Explain how to store BTODs safely out of the sight and reach of all others, especially children.
- Discuss the importance of having access to naloxone with the patient and caregiver, if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.
- Explain what patients should do if they experience side effects.
- Provide induction doses under appropriate supervision.
- Prescribe a limited amount of medication that will last until the patient's next medical appointment.
- Schedule patient appointments commensurate with patient stability (weekly or more frequent medical appointments recommended for the first month).
- Consider "pill/film count"/dose reconciliation.
- Assess whether the patient is receiving counseling/psychosocial support **and if not, encourage them to do so** (See Section VI).
- Assess whether the patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing).
- Continually assess the appropriateness of the maintenance dose (See Section IV).
- Continually assess whether or not the benefits of treatment outweigh the risks.

How should I monitor patients and ensure appropriate dosing of BTODs?

As part of the BTOD REMS, prescribers of BTODs should document safe use conditions and confirm 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 https://www.btodrems.com or by calling 1-855-223-3922.

What information about the safe use of BTODs 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 BTODs 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.**

- Discuss having naloxone available for the emergency treatment of opioid overdose for the patient, household members (including children), or other close contacts at risk for accidental ingestion or opioid overdose.
- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking BTODs. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.
- Advise patients to never give BTODs to anyone else, even if they have the same signs and symptoms. BTODs may cause harm or death.
- Advise patients that BTODs contain an opioid and, like other opioids, can be misused and abused by others. Caution patients to keep their BTODs 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 BTODs is against the law.
- **Use the contents of each BTOD'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 BTOD.
- **Encourage patients to seek psychosocial counseling and support for safe and effective treatment.**

II. BTOD Information Relevant to the REMS Goals

What are BTODs and their uses?

BTODs 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, may deter abuse by the intravenous route of BTODs by people who are dependent on full opioid agonists.

Specific Uses for Formulations of BTODs:

BTODs that contain only buprenorphine are preferred for initiating treatment (**induction**) in patients physically dependent on methadone or long-acting opioids. BTODs that contain buprenorphine with naloxone may be used for **induction** in patients physically dependent on heroin or other short-acting opioids. All BTODs can be used for **maintenance**.

However, in patients with severe hepatic impairment, BTODs that contain only buprenorphine should be used for both **induction** and **maintenance**. Because of a lack of information about the safety of naloxone in pregnancy, BTODs that contain only buprenorphine are also recommended for pregnant patients.

BTODs should be used as part of a complete treatment plan that includes counseling and psychosocial support.[2]

What are the primary differences among the BTODs 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 BTODs 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.

[2] Counseling and other services are important as part of a comprehensive treatment plan, but the provision of medication should not be made contingent upon participation in such services.

Table 1
Corresponding doses of branded and generic BTODs[1]

		BTODs that contain naloxone			
Product Name	Buprenorphine sublingual tablets[2] (generic equivalents of Subutex®)	Buprenorphine/ Naloxone sublingual tablets[2] (generic equivalents of Suboxone®)	Buprenorphine/ Naloxone sublingual films (Suboxone® and generic equivalents)	Buprenorphine/ Naloxone sublingual tablets (Zubsolv®)	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	
	8 mg buprenorphine	8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone	
			12 mg buprenorphine/ 3 mg naloxone	8.6 mg buprenorphine/ 2.1 mg naloxone	
				11.4 mg buprenorphine/ 2.9 mg naloxone	16 mg buprenorphine/ 4 mg naloxone
Route of Administration	Sublingual	Sublingual	Sublingual Buccal	Sublingual	Sublingual

[1] Note that, although the nominal Suboxone sublingual film doses are the same as the generic equivalents of Suboxone sublingual 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.

[2] Subutex and Suboxone tablets are no longer marketed in the U.S., and their approval applications have been withdrawn at the request of the manufacturer.

III. Highlighted Important Safety Information for BTODs

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

- **Store BTODs 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 BTODs.
- **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 medical appointments.
- 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.
- BTODs, like other 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 BTODs by individuals physically dependent on full opioid agonists, or by sublingual or buccal administration before the agonist effects of other opioids have subsided, particularly BTODs that also contain naloxone.
- Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy.
- BTODs 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 BTODs.
- 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 *https://www.fda.gov/medwatch/report.htm.*

IV. Prescribing BTODs

Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose

Because patients being treated for opioid use disorder are at risk for relapse, discuss the importance of having access to naloxone with the patient and caregiver. Also discuss the importance of having access to naloxone if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose.

Inform patients and caregivers of the options for obtaining naloxone.

Educate patients and caregivers on how to recognize the signs and symptoms of an opioid overdose. Explain to patients and caregivers that naloxone's effects are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if naloxone is administered.

In cases of suspected overdose with buprenorphine, advise patients and caregivers that naloxone may also be administered. Higher than normal doses and repeated administration of naloxone may be necessary due to the long duration of action of buprenorphine and its affinity for the mu-opioid receptor.

If the patient will have naloxone, also advise patients and caregivers:

- How to treat with naloxone in the event of an opioid overdose
- To tell family and friends about their naloxone and to keep it in a place where family and friends can easily access it in an emergency
- To read the Patient Information (or other educational material) that will come with their naloxone. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Patient-Specific Dosing

Induction and maintenance doses are dependent on many different factors and should be titrated based on individual patient response.

Refer to the Prescribing Information (PI) for detailed dosing information for each of the BTODs.

Managing Patients on BTODs

How should I schedule medical appointments: how much involvement should I have?

Patient appointments should be scheduled at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. BTODs should be prescribed in consideration of the frequency of appointments. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up appointments. 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 appointments may be appropriate. A once-monthly appointment 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 BTODs by the patient
4. The 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 BTODs 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 Substance Abuse and Mental Health Services Administration (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 BTODs without consulting their prescriber. Advise patients seeking to discontinue treatment with BTODs 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 BTODs, 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 BTODs 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.
- As your patients progress beyond induction to a stabilized dose, consider a longer-term prescription to be taken at home. When determining the quantity to be prescribed, you should consider your patient's level of stability, the security of their 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 is an opioid and, like 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 one aspect of treatment and should be used as part of a complete treatment plan that includes counseling and psychosocial support. Prescribers are encouraged to refer patients to such support and counseling for safe and effective treatment.

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 preferable for the counselor to partner with the prescriber in providing care. The counselor can provide an additional measure of monitoring for adherence and treatment response.

Although counseling and other services are important as part of a comprehensive treatment plan, provision of medication should not be made contingent upon participation in such services.

VII. Additional Information on Treating Opioid Addiction with BTODs

Refer to the package insert for Prescribing Information, which can be found at *https://www.btodrems.com*.

Additional recommendations may be found in treatment guidelines available free from the Center for Substance Abuse Treatment (CSAT) at the SAMHSA website. Additional information is also available on the main 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 (*https://www.asam.org*)
- American Academy of Addiction Psychiatry website (*https://www.aaap.org*)
- Providers Clinical Support System for Medication Assisted Treatment (*https://pcssnow.org/*)

For more information:

https://www.btodrems.com

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

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