BTOD|REMS

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

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

# Important Drug Safety Information for Pharmacists

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

# TABLE OF CONTENTS

## I. BTOD REMS

The purpose of this brochure is to provide pharmacists with information about the **R**isk **E**valuation and **M**itigation **S**trategy (REMS) for 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 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

### What action should I take as a pharmacist to comply with the BTOD REMS?

As part of the REMS, pharmacists dispensing BTODs must supply the Medication Guide with each prescription. The Medication Guide will be provided with the product and is also available by going online to *https://www.btodrems.com* or calling 1-855-223-3922.

As a pharmacist, you will play an important role in ensuring that BTODs are used safely and appropriately. Each time you fill a prescription for a BTOD, make sure to:

- Explain how to store BTODs safely **out of the sight and reach of all others, especially children.**
- 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) to assess for appropriateness of co-prescribing.
- Keep in mind that a limited supply of BTODs should be dispensed during the initiation of therapy. This is due to the need of prescribers to closely and frequently assess the patient's 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 BTODs, including what to do if patients experience side effects.
- Educate patients and caregivers on how to recognize opioid overdose and emphasize the importance of getting emergency medical help right away.
- Remind patients who are picking up induction doses to follow up as directed with the prescriber's office.
- Provide appropriate patient counseling on safe use of BTODs 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 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 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 of BTODs by people who are dependent on full opioid agonists by the intravenous route.

***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. Products 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.[1]**

### 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.

[1] 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[3] | | |
|---|---|---|---|---|
| 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®) |
| 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 |
| Route of Administration | Sublingual | Sublingual | Sublingual Buccal | 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.

[3] Cassipa films are no longer marketed in the U.S., and Cassipa's approval application has been withdrawn at the request of the manufacturer.

## III. Highlighted Important Safety Information for BTODs

This section of the brochure highlights important safety information to consider when prescribing or dispensing BTODs. **Please refer to the Prescribing Information (PI) for detailed safety-related information for 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 an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose.
- Caution patients about the risk of driving or operating hazardous machinery 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 *www.fda.gov/medwatch/report.htm.*

## IV. Dispensing Prescriptions for BTODs

**Important Information to Consider Before Filling Prescriptions for BTODs**

### Who is qualified to prescribe BTODs?

Any healthcare provider who is authorized by the DEA to prescribe schedule III controlled substances may be qualified to prescribe BTODs if permitted by applicable state law.

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

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

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

If you are concerned about the validity of the prescription for any reason, including multiple prescriptions for a single patient, 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: Substance Abuse and Mental Health Services Administration (SAMHSA)/Center for Substance Abuse Treatment (CSAT) at 1-866-BUP-CSAT (1-866-287-2728) or by email: *infobuprenorphine@samhsa.hhs.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*).

### 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 BTOD to your pharmacy, any redisclosure of that patient-identifying information by the *pharmacy* is prohibited without the patient's signed consent.

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

- The 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 they can revoke this consent at any time and that this revocation can be verbal
- The date and terms under which the consent expires
- The patient's dated signature

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

### Are there any special storage, record keeping, or other requirements associated with BTODs?

BTODs are schedule III controlled substances; therefore, BTODs are subject to certain federal regulations covering areas such as record keeping, inventory, proper dispensing, and disposal. 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.pharmacy* for links to individual state boards of pharmacy.

### 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.

## V. Where Can I Get More Information on Treating Opioid Addiction With BTODs?

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 is available through numerous sources, including but not limited to:

- SAMHSA website (*www.samhsa.gov*)
- American Society of Addiction Medicine website (*www.asam.org*)
- American Academy of Addiction Psychiatry website (*www.aaap.org*)

**For more information:**

***https://www.btodrems.com***

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

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