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 PHARMACISTS

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I. BTOD 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 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 substances, 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 Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS Program:

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

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

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

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.
- 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 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 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 of buprenorphine-containing products by people who are dependent on full opioid agonists by the intravenous route.

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 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®)
Dose Strengths Available				0.71 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	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
		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 sublingual film doses are the same as the Suboxone sublingual tablets and generic equivalent tablets, not all strengths and combina ions 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 (FPI) 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 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 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.

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.

DEA regulations require that this number, along with the existing DEA registration number, is included on all prescriptions for buprenorphine-containing products for the treatment of opioid dependence.

What if I get a prescription from a doctor who does not have a special DEA identification number?

Call that prescriber for clarification and confirm that the prescriber has submitted a Notification of Intent form to SAMHSA. The DEA has developed regulations that require this number, along with the prescriber's existing DEA registration number, to be included on all prescriptions issued for the treatment of opioid dependence.

Most prescribers will make arrangements to obtain the identification number before prescribing buprenorphine-containing products, but in rare cases, a prescriber may need to write a prescription before the number has been issued. This is allowed under DATA 2000, provided the prescriber has notified SAMHSA of his/her intention to begin treating a patient immediately.

How can I verify that a prescription is legitimate?

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

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

What should I do if I am seeing prescriptions from a single prescriber that seem to exceed the patient limit?

Prescribers agree to treat no more than 30 patients at a time during the first year of providing buprenorphine treatment. After a year, their patient limit may be increased to 100 patients.

If you are concerned about the validity of the prescription for any reason, including exceeding the patient limit, begin by contacting the prescriber for clarification. In some cases, the prescriber needs the patient's consent to discuss specific patient issues.

You can also contact: SAMHSA/CSAT at 1-866-BUP-CSAT (1-866-287-2728) or by email: info@buprenorphine.samhsa.gov; DEA (www.deadiversion.usdoj.gov); and the State Board of Medicine (a list of contact numbers may be found at this website: (www.fsmb.org/directory_smb.html).

Are there confidentiality issues I should be aware of related to substance abuse treatment?

People with opioid dependence are more likely to seek and continue with treatment when they know their treatment will be held in strict confidence.

For this reason, federal regulations protect the privacy of patients' medical information, namely Title 42 Part 2 of the Code of Federal Regulations (42 CFR Part 2) and the Health Insurance Portability and Accountability Act (HIPAA).

42 CFR Part 2 states that any patient-identifying information pertaining to treatment for substance abuse must be handled with a greater degree of confidentiality than patients' general medical information.

Under 42 CFR Part 2, before a prescriber can disclose any information to a third party about a patient's treatment for substance abuse, that prescriber must first obtain the patient's signed consent.

When a prescriber directly transmits a prescription for a buprenorphine-containing product to your pharmacy, any redisclosure of that patient-identifying information by the *pharmacy* is prohibited without the patient's signed consent.

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

- Patient's name, prescriber's name, pharmacist's name
- Purpose of the disclosure; recipient of the disclosure
- What information will be released
- An indication that the patient understands he/she can revoke this consent at any time and that this revocation can be verbal
- The date and terms under which the consent expires
- Patient's dated signature

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

Are there any special storage, record keeping, or other requirements associated with buprenorphine-containing products?

Buprenorphine-containing products are Schedule III controlled substances; therefore, buprenorphine-containing products are subject to certain federal regulations covering areas such as record keeping, inventory, proper dispensing and disposal. These are explained in the DEA's Pharmacist's Manual, which can be found at www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html. Many states have their own additional requirements for pharmacists dispensing controlled substances. Be sure to check with the appropriate authority in your state. For more information, visit the website of the National Association of Boards of Pharmacy at www.nabp.net for links to individual state boards of pharmacy.

V. WHERE CAN I GET MORE INFORMATION ON TREATING OPIOID ADDICTION WITH BUPRENORPHINE-CONTAINING PRODUCTS?

Refer to the package insert of the product you are dispensing for full information on the adverse reactions seen during the clinical trials using buprenorphine for opioid dependence treatment.

General information about buprenorphine treatment and the treatment of addiction are available through numerous sources, including but not limited to:

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

For more information:

www.btodrems.com

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

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