OFFICE-BASED BUPRENORPHINE THERAPY FOR OPIOID DEPENDENCE:

IMPORTANT INFORMATION FOR PHARMACISTS

BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS
I. INTRODUCTION

The purpose of this brochure is to provide pharmacists with information about the Risk Evaluation and Mitigation Strategy (REMS) for buprenorphine-containing products and the important safety issues and messages needed to counsel patients about its safe use. This REMS applies to buprenorphine-containing oral transmucosal products indicated for the treatment of opioid dependence and buprenorphine-containing products indicated for the treatment of opioid dependence with the same types of safety concerns as the oral transmucosal products (buprenorphine-containing products”). 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 products covered in this REMS are:

- 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 are buprenorphine-containing products?

Buprenorphine-containing products are available both as products containing the single active ingredient, buprenorphine, and products that combine buprenorphine with a second ingredient, naloxone.

Buprenorphine-containing products containing the single active ingredient buprenorphine are indicated for the treatment of opioid dependence and are preferred for induction.

Some buprenorphine products include a second active ingredient, naloxone HCI, intended to deter individuals from abusing buprenorphine-containing products by the intravenous route. Sublingual tablet formulations containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. Suboxone sublingual film and Zubsolv sublingual tablets contain buprenorphine with naloxone and is indicated for the induction of patients physically dependent on heroin or other short-acting opioids as well as for maintenance. However, buprenorphine-only products are preferred for patients physically dependent on methadone or long-acting opioids as per approved labeling.

The following buprenorphine and naloxone combination products are indicated for the maintenance treatment of opioid dependence after initial induction:

- buprenorphine/naloxone sublingual tablets (generic equivalents of Suboxone®)
- Zubsolv sublingual tablets
- Bunavail buccal film
- Suboxone sublingual film

Therefore, while you may see prescriptions for small amounts of buprenorphine alone presented for induction doses, you should expect the majority of prescriptions to be for buprenorphine with naloxone.

Buprenorphine-containing products are controlled as Schedule III narcotics under the Controlled Substances Act.

Patients being switched between different formulations should be started on the corresponding dose (as shown in Table 2 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.

Available Dosage Strengths:

| Table 1 |
|-----------------|-------------------------------------|
| Subutex (Buprenorphine sublingual tablets), including generic equivalents: | 2 mg buprenorphine/8 mg naloxone |
| Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents: | 2 mg buprenorphine/0.5 mg naloxone/6 mg buprenorphine/2 mg naloxone |
| Zubsolv (Buprenorphine and naloxone sublingual tablets): | 1.4 mg buprenorphine/0.36 mg naloxone/2.5 mg buprenorphine/0.71 mg naloxone |
| | 5.7 mg buprenorphine/1.4 mg naloxone/6.6 mg buprenorphine/2.1 mg naloxone |
| Suboxone sublingual film (Buprenorphine and naloxone sublingual film): | 2 mg buprenorphine/0.5 mg naloxone/4 mg buprenorphine/1 mg naloxone |
| | 8 mg buprenorphine/2 mg naloxone/12 mg buprenorphine/3 mg naloxone |
| Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film): | 2.1 mg buprenorphine/0.3 mg naloxone/4.2 mg buprenorphine/0.7 mg naloxone |
| | 6.3 mg buprenorphine/1 mg naloxone/ |

When are buprenorphine-containing products prescribed?

Buprenorphine-only sublingual tablets (Subutex® and generic equivalents) are indicated for the treatment of opioid dependence and are preferred for induction.

The Suboxone sublingual film and Zubsolv sublingual tablets may be used for induction in patients physically dependent on heroin or other short-acting opioids as well as for maintenance. However, buprenorphine-only products are preferred for patients physically dependent on methadone or long-acting opioids as per approved labeling.

The following buprenorphine and naloxone combination products are indicated for the maintenance treatment of opioid dependence after initial induction:

1. Buprenorphine hydrochloride sublingual tablets marketed under the trade name Subutex® are covered under the Subutex and Suboxone REMS programs.
2. 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 for Suboxone tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice versa.

Reference ID: 3804294
Table 2

<table>
<thead>
<tr>
<th>Corresponding doses of buprenorphine products that contain naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboxone sublingual tablets, including generic equivalents</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>2mg buprenorphine/0.5 mg naloxone</td>
</tr>
<tr>
<td>4mg buprenorphine/1 mg naloxone</td>
</tr>
<tr>
<td>8mg buprenorphine/2 mg naloxone</td>
</tr>
<tr>
<td>12mg buprenorphine/3 mg naloxone</td>
</tr>
<tr>
<td>114mg buprenorphine/29.3 mg naloxone</td>
</tr>
</tbody>
</table>

What is my role with regard to 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 1-866-229-3922.

What is the role of the pharmacist in ensuring safe use of buprenorphine-containing products?
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 DATA2000
- 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
- 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 (see Section VI. Patient Information)
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

II. REMS – RISK EVALUATION AND MITIGATION STRATEGY

What is a REMS?
A REMS is a strategy to manage a known or potential risk associated with a drug. A REMS can include, among other strategies, a Medication Guide, a communication plan, and elements to assure safe use.

Is there a REMS for buprenorphine-containing products?
Yes, 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, particularly risks of accidental overdose, misuse, and abuse.

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

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

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 Full Prescribing Information (FPI) for detailed safety-related information for buprenorphine-containing products.

Abuse Potential of Buprenorphine-Containing Products

Are buprenorphine-containing products abusable?
Yes, buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when dispensing buprenorphine in situations when there is a concern about an increased risk of misuse, abuse, or diversion. All healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

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.
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy and proper handling and storage of the medication by the prescriber and patient are appropriate measures that help to limit abuse of opioid drugs.

Due to the partial agonist properties of buprenorphine, buprenorphine-containing products may precipitate opioid withdrawal signs and symptoms in persons dependent on full opioid agonists if administered before the agonist effects of the opioid have subsided. However, buprenorphine products that contain naloxone are highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Therefore, to discourage misuse or abuse, it is highly recommended that, after induction, for unsupervised administration, buprenorphine with naloxone rather than buprenorphine alone is prescribed whenever feasible.

However, pharmacists should also be aware that some opioid-dependent persons can and do abuse buprenorphine/naloxone combinations by the intravenous or intranasal routes. This is especially true for opioid-dependent persons with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine.

Can buprenorphine-containing products cause dependence?

Yes, buprenorphine is a partial agonist at the mu-opioid receptor. Chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. If cessation of therapy is indicated, it is appropriate to taper the buprenorphine dose, rather than abruptly discontinue the medication. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing buprenorphine in situations where there is an increased concern about the possibility of misuse, diversion, or abuse.

How can patients prevent accidental exposure to buprenorphine-containing products in children?

Patients should be instructed to keep buprenorphine-containing products in a secure place, out of the sight and reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed accidentally to a buprenorphine-containing product, seek immediate urgent medical attention.

What is an appropriate medical response to an overdose on a buprenorphine-containing product?

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone hydrochloride may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

Contraindications

- Hypersensitivity to buprenorphine and, in the case of combination products, naloxone

Warnings and Precautions

- 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
- 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
- Store buprenorphine-containing products safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- 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 2mg sublingual dose
- Caution patients about the risk of driving or operating hazardous machinery
- For buprenorphine/naloxone combination products:
  - Not recommended in patients with severe hepatic impairment
  - Not recommended for initiation of treatment (induction) in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. However, buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine’s efficacy.
Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists

IV. DISPENSING PRESCRIPTIONS FOR BUPRENORPHINE-CONTAINING PRODUCTS

This section discusses important information to consider before filing prescriptions for buprenorphine-containing products.

Who is qualified to prescribe buprenorphine-containing products?


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, be 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 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...
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Important Information for Pharmacists

V. SUPPLYING AND ADMINISTERING BUPRENORPHINE-CONTAINING PRODUCTS

How are buprenorphine-containing products supplied?

| Subutex (Buprenorphine sublingual tablets), including generic equivalents: | 2 mg buprenorphine | 8 mg buprenorphine |
| Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents: | 2 mg buprenorphine | 0.5 mg naloxone | 8 mg buprenorphine | 2 mg naloxone |
| Zubsolv (Buprenorphine and naloxone sublingual tablets): | 1.4 mg buprenorphine | 0.35 mg naloxone | 2.9 mg buprenorphine | 0.71 mg naloxone | 5.7 mg buprenorphine | 1.4 mg naloxone | 8.6 mg buprenorphine | 2.1 mg naloxone | 11.4 mg buprenorphine | 2.9 mg naloxone |
| Suboxone sublingual film (Buprenorphine and naloxone sublingual film): | 2 mg buprenorphine | 0.5 mg naloxone | 4 mg buprenorphine | 1 mg naloxone | 8 mg buprenorphine | 2 mg naloxone | 12 mg buprenorphine | 3 mg naloxone |
| Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film): | 2.1 mg buprenorphine | 0.3 mg naloxone | 4.2 mg buprenorphine | 0.7 mg naloxone | 6.3 mg buprenorphine | 1.1 mg naloxone |

How should buprenorphine with or without naloxone be administered?

For buprenorphine-containing tablets, the patient should place tablets under the tongue until they are dissolved. For doses requiring the use of more than 2 tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than 2 tablets comfortably), place 2 tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

For Bunavail buccal film administration, the patient should use the tongue to wet the inside of the cheek or rinse the mouth with water to moisten the area immediately before placement of Bunavail; open the Bunavail package immediately prior to use as indicated by the instructions, place the Bunavail film near the tip of a dry finger with the text facing up; place the side of the Bunavail film with the text against the inside of the cheek, press and hold the film in place for 5 seconds. Bunavail film(s) adhere to the moist buccal mucosa and should stay in place after this period. If multiple films need to be administered, the patient should immediately apply the next film. Note that when two films are required for one dose, the patient should place one film on the inside of each cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time. The patient should be instructed to avoid manipulating the film(s) with their tongue or finger(s) and avoid drinking or eating food until the film(s) dissolve.

For Suboxone sublingual film, the patient should place the Suboxone film under the tongue. If an additional film is necessary to achieve the prescribed dose, the additional film should be placed sublingually on the opposite side from the first film. If an additional third film is needed, place it sublingually after the first 2 Suboxone sublingual films have dissolved. Place Suboxone sublingual films in a manner to minimize overlapping as much as possible. Keep the films under the tongue, close to the base on the left or right side, until

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.
VI. PATIENT INFORMATION

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

The safety concerns related to the use of buprenorphine-containing products includes, but are not limited to, the following:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking buprenorphine-containing products. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their prescriber.
- Instruct patients to keep buprenorphine-containing products in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to buprenorphine-containing products, medical attention should be sought immediately.
- Advise patients that buprenorphine-containing products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their products in a safe place and to protect them from theft.
- Instruct patients never to give buprenorphine-containing products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away buprenorphine-containing products is against the law.
- Caution patients that buprenorphine-containing products may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken, especially during drug induction and dose adjustments and until they are reasonably certain that buprenorphine-containing products do not adversely affect their ability to engage in such activities.
- Advise patients not to change the dose of buprenorphine-containing products without consulting their prescriber.
- Advise patients to take buprenorphine-containing products once a day as directed.
- Inform patients that buprenorphine-containing products can cause drug dependence of the opioid type. Withdrawal signs and symptoms may occur when the medication is discontinued.
- Advise patients seeking to discontinue treatment with buprenorphine-containing products for opioid dependence to work closely with their prescriber on a tapering schedule, and apprise of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Caution patients that, like other opioids, buprenorphine-containing products may produce orthostatic hypotension in ambulatory individuals.
- Ask patients if other prescription medications, over-the-counter medications or herbal preparations are prescribed or are currently being used.
- Advise patients who become pregnant or are planning to become pregnant, to consult their prescriber regarding the possible effects secondary to using buprenorphine-containing products during pregnancy.
- Buprenorphine and naloxone-containing products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Based on two studies in 13 lactating women, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding; however, oral absorption of naloxone is minimal. Caution should be exercised when buprenorphine-containing products are administered to a nursing woman.
- The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for buprenorphine-containing products and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.
- Advise the nursing mother taking buprenorphine and naloxone-containing products to monitor the infant for increased drowsiness and breathing difficulties.
- Ask patients to inform their family members or other appropriate individuals that, in the event of emergency, the treating prescriber or emergency department staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with buprenorphine-containing products.
- Instruct patients to dispose of unused buprenorphine-containing products as soon as it is no longer needed. Unused tablets and films (after they have been removed from the foil package) should be flushed down the toilet.

VII. WHERE CAN I GET MORE INFORMATION ON TREATING OPIOID ADDICTION WITH BUPRENOPHINE-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.aap.org)