OFFICE-BASED BUPRENORPHINE THERAPY FOR OPIOID DEPENDENCE:

IMPORTANT INFORMATION FOR PRESCRIBERS

BUPRENORPHINE-CONTAINING TRANSMUCOSAL PRODUCTS
Office-Based Buprenorphine Therapy for Opioid Dependence:
Important Information for Prescribers

I. INTRODUCTION

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 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 (hereinafter, “buprenorphine-containing products”). 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 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

This brochure summarizes important safety issues and messages needed to manage and counsel patients about safe use of these products.

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 naloxone.

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

Sublingual tablet formulations containing buprenorphine with naloxone are indicated for the maintenance treatment of opioid dependence. The Suboxone sublingual film and Zubsolv sublingual tablets contain buprenorphine with naloxone and are indicated for the induction of patients physically dependent on heroin or other short-acting opioids (for long-acting opioids, see next section) and maintenance treatment of opioid dependence.

Buprenorphine-containing products are used as 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, indications, 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).

Available Dosage Strengths:

Table 1

| 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 |
| 6.6 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/0.6 mg naloxone |
| 6.3 mg buprenorphine/1 mg naloxone |

Indications:

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 formulation 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 taken 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

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 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.

Reference ID: 3804294
different when patients are switched from tablets to films or vice-versa.
## II. REMS – RISK EVALUATION AND MITIGATION STRATEGY

### What is a Risk Evaluation and Mitigation Strategy (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.

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

### What is my role with regard to 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 diagnostic criteria for opioid dependence
- Discuss the risks associated with buprenorphine-containing products, including those described in the Medication Guide
- 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 safely store the medication out of reach of 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 patients receiving counseling/psychosocial support considered necessary for treatment
- Assess whether patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing)
- Continually assess appropriateness of maintenance dose
- Continually assess whether or not benefits of treatment outweigh the risks

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 provider’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 1-855-223-3022.

### III. HIGHLIGHTED IMPORTANT SAFETY INFORMATION FOR BUPRENOPHINE-CONTAINING PRODUCTS

This section of the brochure highlights important safety information to consider when prescribing buprenorphine-containing products. Refer to the Full Prescribing Information (FPI) for detailed safety-related information for buprenorphine-containing products.

#### Abuse Potential for 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 prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse, misuse, 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. The prescriber may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal request of medication prescribed.
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, clinicians 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. 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.

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

What precautions should I take in my practice to prevent diversion and abuse?

You should 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 strongly recommended that buprenorphine/naloxone products be used when unsupervised administrations are planned.
- As your patient’s 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.
- Establish a relationship with the pharmacies you expect to be filling your prescriptions. Discuss potential diversion problems and controls with them.
- Maintain copies of photo (or other) I.D. and Social Security numbers in patients’ records.
- 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 call back to verify adherence to program rules. In a call back, 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.

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 overdose on 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 naive individuals who received a 2 mg 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.
- For buprenorphine sublingual tablets:
  - Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half compared to patients with normal liver function, and monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.
- Moderate hepatic impairment: Although no dose adjustment is necessary for patients with moderate hepatic impairment, buprenorphine sublingual tablets should be used with caution in these patients and prescribers should monitor patients for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Adverse Reactions

- Adverse events most commonly observed with buprenorphine-containing products are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain. For a complete list of potential adverse events associated with buprenorphine-containing products, please see the Full Prescribing Information.

- 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

Drug Interactions

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing.
- Use caution in prescribing buprenorphine-containing products for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse.

Use in Specific Populations

- Pregnancy: Based on animal data, buprenorphine may cause fetal harm. Buprenorphine-containing products are not indicated for use during pregnancy unless potential benefit justifies potential risk.
- Nursing mothers: Caution should be exercised when buprenorphine-containing products are administered to a nursing woman.
- Safety and effectiveness of buprenorphine-containing products in patients below the age of 16 have not been established.
- Administer these products with caution to elderly or debilitated patients.
- Buprenorphine/naloxone products are not recommended for use in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.
- Buprenorphine-only sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment and a dose adjustment is recommended for patients with severe hepatic impairment.
IV. PRESCRIBING BUPRENORPHINE-CONTAINING PRODUCTS

When should products containing buprenorphine with naloxone be prescribed?

Buprenorphine products that include naloxone are indicated for maintenance treatment of opioid dependence and are preferred over buprenorphine-only products for unsupervised administration. Suboxone sublingual film and Zubsolv sublingual tablet, which contain naloxone, is indicated for the induction of patients physically dependent on heroin or other short-acting opioids (for long-acting opioids, see discussion below and in Introduction Section) and maintenance treatment of opioid dependence.

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, 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 maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal signs and symptoms.

Patients taking methadone or long-acting opioids:

Buprenorphine monotherapy is preferred for induction in patients physically dependent on methadone or long-acting opioids, if taken per approved labeling. Buprenorphine and naloxone combination products have not been evaluated in adequate and well-controlled studies for induction in patients on long-acting opioids, who appear to be more likely to experience precipitated and prolonged withdrawal than those on short-acting opioids.

To avoid inadvertently precipitating opioid withdrawal, induction should be undertaken when clear and obvious signs of withdrawal are evident. A clinical tool to assess withdrawal should be used. For example, the Clinical Opioid Withdrawal Scale (COWS) can be used and a score of >12 should be recorded on the COWS before the first dose is administered.

Patients taking heroin or other short-acting opioids:

Patients physically dependent on heroin or other short-acting opioids may initiate treatment with either a buprenorphine-only sublingual product or with Suboxone sublingual film. At treatment initiation, the dose of buprenorphine-only sublingual product or Suboxone sublingual film should be administered when moderate signs of opioid withdrawal are evident and at least 6 hours after the patient last used short-acting opioids.

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 alone 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:

- Absence of buprenorphine toxicity
- Absence of medical or behavioral adverse effects
- Responsibility handling of buprenorphine-containing product by the patient
- Patient’s compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
- 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 do I manage in-office induction doses without maintaining a supply in my office?

For those prescribers who do not wish to maintain a supply of buprenorphine-containing products in their offices, it is important to develop a good working relationship with your local pharmacies. To ensure that you will be able to exchange information with the pharmacist, such as confirming the validity of your induction prescriptions, it is recommended that you have the patient sign a release of information at the time of the initial office visit. A sample consent form with all the elements required under 42 CFR Part 2.31 is included in Appendix A of this brochure.

On the day of induction, write a prescription only for the induction day’s dosage. Instruct your patient or (if available, a trustworthy family member accompanying the patient) to take the prescription to the pharmacy, have it filled and bring it back to your office for dosing.

It is recommended that you call or fax ahead to the pharmacy to ensure availability of the medication and to reduce patient waiting time. You should instruct the patient not to take the dose until he or she returns to the office. The induction dose will be administered, and he or she will be monitored, in your office. The pharmacist should restate this instruction upon filling the prescription.

Note that it is illegal for prescribers to hold medication in the office that is prescribed for a specific patient. Therefore, you should limit the prescription to one day’s dose, and repeat this method for the
Will prescriptions be valid at any pharmacy, or will I need to refer patients to a specific location?

Prescriptions specifying a buprenorphine-containing product will be valid at any pharmacy authorized by DEA to handle Schedule III controlled substances. However, prior to prescribing buprenorphine-containing products it is essential that you establish a relationship with one or more specific pharmacies in your area that will be in a position to provide your patients with initial doses, as well as instructions for returning to your office for induction and the follow-up prescription.

Generally, a pharmacy near your office is recommended for patient convenience.

What storage and record-keeping requirements are associated with treating patients for opioid dependence with buprenorphine-containing products?

If you wish to maintain a supply of buprenorphine-containing products in your office for the purpose of dispensing to patients during induction, you will be required to keep the medications in a secure environment. According to federal requirement, they must be kept in a securely locked, substantially constructed cabinet. You will also be required to maintain a written record of the disposition of all doses. Usually this can be done with the maintenance of a logbook in which you record all incoming doses and account for each dispensed dose as it is used. This record must be kept current at all times. Additional requirements may be in place in your state. You are also required to take an inventory every 2 years, and to keep records of all receipts.

In addition, prescribers of buprenorphine-containing products should keep accurate and complete records for each patient that include:

1. The medical history and physical examination
2. Diagnostic, therapeutic, and laboratory results
3. Evaluations and consultations
4. Treatment objectives
5. Discussion of risks and benefits
6. All treatments that the patient is receiving
7. Medications (including date, type, dosage, and quantity prescribed and/or dispensed to each patient)
8. A physical inventory of all Schedule III, IV, and V controlled substances on hand that are dispensed by the prescriber in the course of maintenance or detoxification treatment of an individual
9. Instructions and agreements
10. Periodic reviews

Records should remain current and be maintained in an accessible manner and readily available for review. Prescribers must adhere to the special confidentiality requirements of 42 CFR Part 2.

Are there special confidentiality issues I should consider?

Remember that you may be communicating with the pharmacist to verify prescriptions for a particular patient. There are special federal regulations concerning the confidentiality of substance abuse treatment records (42 CFR Part 2), and the privacy of health records (Health Insurance Portability and Accountability Act [HIPAA]). To ensure that you will be able to exchange information with the pharmacist, such as confirming the validity of a prescription for a buprenorphine-containing product, it is recommended that you have the patient sign a release of information at the time of the initial office visit.

A sample consent form with all the elements required under 42 CFR Part 2.31 is included in Appendix A of this brochure. It is particularly important to obtain the patient’s consent if you elect to phone or fax in prescriptions, as this constitutes disclosure of the patient’s treatment. When the prescription is directly transmitted by the prescriber, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42 CFR Part 2.31 does not apply when it is the patient who delivers the prescription to the pharmacist, without direct communication from the prescriber to the pharmacist.

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

Dosing and Administration of 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, and is 11.4 mg buprenorphine/2.8 mg naloxone per day for Zubsolv sublingual tablet, and 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, 17.1 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 are buprenorphine-containing products supplied?

<table>
<thead>
<tr>
<th>Product</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subutex (buprenorphine sublingual tablets), including generic equivalents:</td>
<td>2 mg buprenorphine</td>
</tr>
<tr>
<td>Suboxone (Buprenorphine and naloxone sublingual tablets), including generic equivalents:</td>
<td>2 mg buprenorphine / 0.5 mg naloxone</td>
</tr>
<tr>
<td>Zubsolv (Buprenorphine and naloxone sublingual tablets):</td>
<td>1.4 mg buprenorphine / 0.36 mg naloxone</td>
</tr>
<tr>
<td>Suboxone sublingual film (Buprenorphine and naloxone sublingual film):</td>
<td>2 mg buprenorphine / 0.5 mg naloxone</td>
</tr>
<tr>
<td>Bunavail (Buprenorphine hydrochloride and naloxone hydrochloride buccal film):</td>
<td>2.1 mg buprenorphine / 0.3 mg naloxone</td>
</tr>
</tbody>
</table>

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 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 they are completely dissolved. Suboxone sublingual film should NOT be chewed, swallowed, or moved after placement.

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.

Discontinuing Therapy with Buprenorphine-Containing Products

What can I tell patients who wish to discontinue treatment?

Patients should be advised not to change the dose of buprenorphine-containing products without consulting their prescriber. Patients seeking to discontinue treatment with buprenorphine-containing products for opioid dependence should be apprised of the potential to relapse or 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, it may be appropriate to taper the dose of these products, rather than abruptly discontinue it. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

V. 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. Because it is such a crucial element, DATA2000 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.

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

Review the contents of the Medication Guide, in its entirety, with each patient, including the following:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants.
(including alcohol) while taking any buprenorphine-containing product. 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. If a child is exposed to one of these 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 induction and dose adjustments and until patients are reasonably certain that therapy with a buprenorphine-containing product does not adversely affect their ability to engage in such activities.

- Advise patients not to change the dose of the buprenorphine-containing product without consulting their prescriber.

- Advise patients to take the buprenorphine-containing product once a day as directed.

- Inform patients that the 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 the buprenorphine-containing product for opioid dependence to work closely with their prescriber on a tapering schedule and apprise them 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 prescriber or currently being used.

- Advise patients who become pregnant, or are planning to become pregnant, to consult their prescriber regarding the possible effects of using buprenorphine-containing products during pregnancy.

- Buprenorphine-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-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 a buprenorphine-containing product.

- Instruct patients to dispose of unused buprenorphine-containing product 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.

VI. WHERE CAN I GET MORE INFORMATION ON TREATING PATIENTS WITH BUPRENOPHINE-CONTAINING PRODUCTS?

Refer to the package insert for Full 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. Additional information is also available on the CSAT Buprenorphine Information Center website at http://buprenorphine.samhsa.gov.

General information about buprenorphine treatment and treatment of addiction are 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.aap.org)
- Physician Clinical Support System-Buprenorphine (http://pcssb.org)
APPENDIX A
Sample 42 CFR Part 2.31 Consent Form

1. I (name of patient)

2. Authorize Dr.

3. To disclose any information needed to confirm the validity of my prescription and for submission for payment for the prescription.

4. To the dispensing pharmacy to whom I present my prescription or to whom my prescription is mailed, sent/faxed, as well as to third party payers.

5. For the purpose of assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.

6. Date (on which this consent is signed)

7. Signature of patient

8. Signature of parent or guardian (where required)

9. Signature of person authorized to sign in lieu of the patient (where required)

10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specify date, event, or condition, i.e., termination of treatment)

Notice to accompany disclosure:
Each disclosure made with the patient’s written consent must be accompanied by the following written statement:

This information has been disclosed to you from records protected by Federal confidentiality rules (42 CFR Part 2). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the person to whom it pertains or as otherwise permitted by 42 CFR Part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose. The Federal rules restrict any use of the information to criminally investigate or prosecute any alcohol or drug abuse patient.