Office-Based Buprenorphine Therapy for Opioid Dependence:

Important Information for Prescribers

SUBOXONE®
(buprenorphine and naloxone)
sublingual film CIII

SUBOXONE®
(buprenorphine and naloxone)
sublingual tablets CIII

SUBUTEX®
(buprenorphine)
sublingual tablets CIII

Collectively Referred to as:
Buprenorphine-Containing Products
1. Introduction

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) for prescribers of SUBOXONE (buprenorphine and naloxone) sublingual film CIII, SUBOXONE (buprenorphine and naloxone) sublingual tablets CIII, and SUBUTEX (buprenorphine) sublingual tablets CIII who are certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). Hereinafter, these three products will be referred to as “buprenorphine-containing products”.

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. 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 because the care of these patients is subject to specific requirements under these regulations.

This brochure summarizes important safety issues and information needed to manage and counsel patients about safe use of buprenorphine-containing 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. Some buprenorphine-containing products include a second active ingredient, naloxone HCl, 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. The SUBOXONE sublingual film formulation contains buprenorphine with naloxone and is 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. (See Section IV. Prescribing Buprenorphine-Containing Products for further details).

Buprenorphine-containing products are used as part of a complete treatment plan, including counseling, behavioral therapy and/or 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 |
| Zubsov (Buprenorphine and naloxone sublingual tablets): | 1.4 mg buprenorphine / 0.36 mg naloxone 2.0 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 (Buprenorphine and naloxone sublingual film): Note: SUBOXONE film may also be administered by the buccal route. | 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 |
**Indications:**

SUBUTEX sublingual tablets and generic equivalents are indicated for the treatment of opioid dependence and are preferred for induction.

The SUBOXONE sublingual film formulation, indicated for the treatment of opioid dependence, 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 initiating treatment in patients physically dependent on methadone or long-acting opioids taken as per approved labeling. Additionally, buprenorphine-only products should be used in patients with severe hepatic impairment and in pregnant patients.

SUBOXONE sublingual tablets, including generic equivalents, SUBOXONE sublingual film, Bunavail buccal film and Zubsolv sublingual tablets are indicated for the maintenance treatment of opioid dependence after induction.

**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) 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

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**Table 2**

Corresponding doses of buprenorphine products that contain naloxone

<table>
<thead>
<tr>
<th>SUBOXONE sublingual tablets including generic equivalents</th>
<th>SUBOXONE sublingual film</th>
<th>Zubsolv sublingual tablets</th>
<th>Bunavail buccal films</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg buprenorphine / 0.5 mg naloxone</td>
<td>2 mg buprenorphine / 0.5 mg naloxone</td>
<td>1.4 mg buprenorphine / 0.36 mg naloxone</td>
<td></td>
</tr>
<tr>
<td>4 mg buprenorphine / 1 mg naloxone</td>
<td>2.9 mg buprenorphine / 0.71 mg naloxone</td>
<td>2.1 mg buprenorphine / 0.3 mg naloxone</td>
<td></td>
</tr>
<tr>
<td>8 mg buprenorphine / 2 mg naloxone</td>
<td>8 mg buprenorphine / 2 mg naloxone</td>
<td>5.7 mg buprenorphine / 1.4 mg naloxone</td>
<td>4.2 mg buprenorphine / 0.7 mg naloxone</td>
</tr>
<tr>
<td>12 mg buprenorphine / 3 mg naloxone</td>
<td>8.6 mg buprenorphine / 2.1 mg naloxone</td>
<td>6.3 mg buprenorphine / 1 mg naloxone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.4 mg buprenorphine / 2.9 mg naloxone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 combinations of the films are bioequivalent to the generic equivalent or Zubsolv tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

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Please see www.innovatREMS.com for more information.
How is SUBOXONE sublingual film different from the buprenorphine and naloxone sublingual tablet formulation?

The primary difference is the delivery mechanism of the SUBOXONE sublingual film formulation. SUBOXONE sublingual film contains buprenorphine and naloxone, similar to the buprenorphine and naloxone tablet formulation. The dosage strengths for SUBOXONE sublingual film are: 2/0.5 mg, 4/1 mg, 8/2 mg, and 12/3 mg.

Patients being switched between buprenorphine/naloxone sublingual tablets and SUBOXONE sublingual film should be started on the corresponding dosage as the previously administered product (see Table 2). However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual film are bioequivalent to the buprenorphine and naloxone sublingual tablets as observed in pharmacokinetic studies. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablet formulations to SUBOXONE sublingual film or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

The sizes and the compositions of the four units of SUBOXONE sublingual film, i.e., 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units, are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE sublingual film to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacists should not substitute one or more film strengths for another without approval of the prescriber.

<table>
<thead>
<tr>
<th>SUBOXONE sublingual film unit strength (buprenorphine/naloxone)</th>
<th>SUBOXONE sublingual film unit dimensions</th>
<th>Buprenorphine Concentration % (w/w)</th>
<th>Naloxone Concentration % (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/0.5 mg</td>
<td>22.0 mm x 12.8 mm</td>
<td>5.4</td>
<td>1.53</td>
</tr>
<tr>
<td>4 mg/1 mg</td>
<td>22.0 mm x 25.6 mm</td>
<td>5.4</td>
<td>1.53</td>
</tr>
<tr>
<td>(2 times the length of the 2 mg/0.5 mg unit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 mg/2 mg</td>
<td>22.0 mm x 12.8 mm</td>
<td>17.2</td>
<td>4.88</td>
</tr>
<tr>
<td>12 mg/3 mg</td>
<td>22.0 mm x 19.2 mm</td>
<td>17.2</td>
<td>4.88</td>
</tr>
<tr>
<td>(1.5 times the length of the 8 mg/2 mg unit)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets?

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with these buprenorphine products outweigh the potential risks.

The goals of the REMS for SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets are to:

1. Mitigate the risks of accidental overdose, misuse, and abuse
2. Inform prescribers, pharmacists, and patients of the serious risks associated with the use of SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets

What is my role with regard to the SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets 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 patient meets diagnostic criteria for opioid dependence
- Discuss the risks associated with SUBOXONE sublingual film, including those described in the professional labeling and the Medication Guide
- Provide induction doses under appropriate supervision
- Prescribe a limited amount of medication to the patient; only that which will last until the next visit
- Explain how to safely store the medication out of the sight and 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 a patient is receiving counseling/psychosocial support considered necessary for treatment
- Assess whether a 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 SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets REMS, prescribers of these products should document safe use conditions and that each patient has received required clinical monitoring using the Appropriate Use Checklist, or by using another method/system (e.g., electronic health record) specific to the prescriber’s office practice. This can be retained in the records of each patient. Additional copies of the Appropriate Use Checklist can be obtained online at www.IndiviorREMS.com or by calling 1-877-782-6966.
III. Highlighted Important Safety Information for Buprenorphine-Containing Products

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

Abuse Potential of Buprenorphine-containing products

Are buprenorphine-containing products abusive?

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 buprenorphine in situations when there is a concern 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 the date, dose, quantity, frequency of refills, and renewal request of medication prescribed.

Prescribers should also check state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy and proper handing 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. SUBUTEX (buprenorphine only) does not contain a naloxone component. 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 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 due 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 or dispensing 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 SUBOXONE also contains 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 whenever unsupervised administration is planned.

- As your patients progress beyond induction to a stabilized dose, consider a longer-term prescription of a buprenorphine-containing product. When determining the quantity of a 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 callback to verify adherence to program rules. In a callback, the patient receives an unannounced phone call and must show up at the prescriber’s office within a reasonable period (e.g., 24 to 36 hours) with all prescribed medications. In this case, the amount of medication remaining must correspond to the amount expected based on prescribed dosing. If this program is implemented, prescribers should clearly state their policy to patients in advance.

  Buprenorphine, 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 buprenorphine-containing products, seek immediate urgent medical attention.

What is an appropriate medical response to an overdose of 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.
What are other important safety considerations for prescribers of buprenorphine-containing products?

**Contraindications**

- Hypersensitivity to buprenorphine or 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 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.

- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy.
- Buprenorphine-containing products covered under this REMS are not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose of buprenorphine.
- Caution patients about the risk of driving or operating hazardous machinery while taking buprenorphine-containing products.
- 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. 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 of 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

What are the commonly observed adverse events of SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBUTEX sublingual tablets?

- Adverse events commonly observed with the sublingual/buccal administration of SUBOXONE sublingual film were oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. For a complete list of potential adverse events associated with SUBOXONE sublingual film, please see Full Prescribing Information.

- Adverse events most commonly observed with SUBOXONE sublingual tablets were headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. For a complete list of potential adverse events associated with SUBOXONE sublingual tablet, please see the Full Prescribing Information.

- Adverse events most commonly observed with the sublingual administration of the SUBUTEX sublingual tablets during clinical trials and post-marketing experience were 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 for each product.

- To report SUSPECTED ADVERSE REACTIONS contact:
  - Indivior Inc. at 1-877-782-6986 or
  - FDA MedWatch program by phone at 1-800-FDA-1088, or online at www.fda.gov/medwatch/report.htm

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.

- 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. 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.

- Safety and effectiveness of buprenorphine-containing products in patients below the age of 16 have not been established.

- Administer buprenorphine-containing products with caution to elderly or debilitated patients.

- Buprenorphine and naloxone containing products are not recommended for use in patients with severe hepatic impairment and may be used with caution in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone.

- Buprenorphine 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.

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.

Please see www.indivorREMS.com for more information.
IV. Prescribing Buprenorphine-Containing Products

When should products containing buprenorphine with naloxone be prescribed?

Buprenorphine products that contain naloxone are preferred over buprenorphine-only products for unsupervised administration. SUBOXONE sublingual film, which includes naloxone, may be used for initiation of treatment in 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 heroin or other short-acting opioids:

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

Patients taking methadone or long-acting opioids:

Buprenorphine monotherapy is preferred for induction in patients physically dependent on methadone or long-acting opioids. 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.
**Dosing and Administration of buprenorphine-containing products**

How should patients be induced with buprenorphine-containing products?

**SUBUTEX:**
SUBUTEX treatment may be initiated with a single daily dose of 8 mg, titrating to 16 mg on day 2; or the regimen below may be followed.

**SUBOXONE FILM:**
On Day 1, an induction dosage of up to 8 mg/2 mg SUBOXONE sublingual film is recommended. Clinicians should start with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg and may titrate upwards in 2 mg/0.5 mg or 4 mg/1 mg increments (at approximately 2-hour intervals, under supervision) to 8 mg/2 mg based on the control of acute withdrawal signs. On Day 2, a single dose of up to 16 mg/4 mg SUBOXONE sublingual film is recommended.

Because the exposure to naloxone is somewhat higher after buccal than after sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimize exposure to naloxone, to reduce the risk of precipitated withdrawal.

**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 for Zubsov sublingual tablets, 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 buprenorphine per day for SUBOXONE sublingual tablets and sublingual film, including generic equivalents, 17.1 mg buprenorphine per day for Zubsov, and 12.6 mg buprenorphine 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 4**

| 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 |

| Zubsov (Buprenorphine and naloxone sublingual film): |
| 1.4 mg buprenorphine / 0.36 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 (Buprenorphine and naloxone sublingual film): |
| 2 mg buprenorphine / 0.6 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 |

Please see www.indvlorREMS.com for more information.
How should buprenorphine with or without naloxone be administered?

SUBOXONE sublingual film can be administered sublingually or buccally as described below.

SUBOXONE sublingual film must be administered whole. Do not cut, chew, or swallow SUBOXONE sublingual film. Swallowing the film reduces the bioavailability of the drug. SUBOXONE sublingual film should NOT be moved after placement. Proper administration technique should be demonstrated to the patient. See the Medication Guide for additional administration instructions.

**Sublingual Administration**

Place a film under the tongue close to the base on the left or right side. If an additional film is necessary to achieve the prescribed dose, place an additional film sublingually on the opposite side from the first film. Place the film in a manner to minimize overlapping as much as possible. The film must be kept under the tongue until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side after the first 2 films have dissolved.

**Buccal Administration**

Place one film on the inside of the right or left cheek. If an additional film is necessary to achieve the prescribed dose, place an additional film on the inside of the opposite cheek. The film must be kept on the inside of the cheek until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it on the inside of the right or left cheek after the first two films have dissolved.

SUBUTEX sublingual tablets and generic equivalents, SUBOXONE sublingual tablets and generic equivalents, and Zubsolv sublingual tablets should be placed 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 Bupenall buccal film administration, the patients 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 Bupenall; open the Bupenall package immediately prior to use as indicated by the instructions; place the Bupenall film near the tip of a dry finger with the text facing up; place the side of the Bupenall film with the text against the inside of the cheek; press and hold the film in place for 5 seconds. Bupenall 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 should avoid drinking or eating food until the film(s) dissolve.
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 with naloxone 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:

1. Absence of buprenorphine toxicity
2. Absence of medical or behavioral adverse effects
3. Responsible handling of buprenorphine-containing products by the patient
4. Patient’s compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use)

If treatment goals are not being achieved, the prescriber should reevaluate the appropriateness of continued treatment. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

How should I manage patients who are not compliant with therapy?

Prescribers will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention, such that the prescriber does not feel that he or she has the expertise to manage the patient. In such cases, the prescriber may want to assess whether to refer the patient to a specialist and/or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

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 booklet with this booklet (see page 32).

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 reiterate 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 first several days of treatment before providing a prescription for several days’ supply at one time.
Will prescriptions be valid at any pharmacy, or will I need to refer patients to a specific location?

Prescriptions specifying buprenorphine-containing products 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 requirements, 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 for the treatment of opioid dependence 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 buprenorphine-containing product prescription, 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 with this booklet (see page 32). It is particularly important to obtain the patient’s consent if you elect to phone, fax in, or e-prescribe 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).

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 to 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, DATA 2000 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, contingency management, 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 should I communicate 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, urgent medical attention should be sought immediately.

Please see www disciplerm.rems.com for more information.
> 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 buprenorphine-containing products without consulting their prescriber.

> After treatment induction, 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 them of the potential to and harm associated with 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 of using buprenorphine-containing products during pregnancy.

> Advise nursing mothers 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 healthcare provider 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 SUBOXONE sublingual film as soon as it is no longer needed. Unused films should be removed from the foil pouch and then flushed down the toilet. Unused SUBOXONE sublingual tablets and SUBUTEX sublingual tablets may also be disposed by flushing them down the toilet.

VI. Where Can I Get More Information on Treating Opioid Dependence With buprenorphine-containing products?

Refer to the package insert for Full Prescribing Information which can be found at www.IndiviorREMS.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://www.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.aaap.org)

> Physician Clinical Support System - Buprenorphine (www.pcssmat.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 called/sent/faxed, as well as to third party payors.

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 that 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)

________________________________________