Office-Based Buprenorphine Therapy for Opioid Dependence:

Important Information for Pharmacists

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
I. Introduction

The purpose of this brochure is to provide pharmacists with information about the Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE (buprenorphine and naloxone) sublingual film CIII, SUBOXONE (buprenorphine and naloxone) sublingual tablets CIII, and SUBUTEX (buprenorphine) sublingual tablets CIII and the important safety issues and messages needed to counsel patients about its safe use. 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.

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.

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 |
| ZubSolv (Buprenorphine and naloxone sublingual tablets): | 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): 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 |

Reference ID: 0322150
**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 Zubsov sublingual tablets are indicated for the maintenance treatment of opioid dependence after initial 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

**Table 2**

<table>
<thead>
<tr>
<th>SUBOXONE sublingual tablets including generic equivalents</th>
<th>SUBOXONE sublingual film</th>
<th>Zubsov 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></td>
<td>2.1 mg buprenorphine / 0.3 mg naloxone</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 Zubsov tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.
When are buprenorphine-containing products prescribed?

Buprenorphine with naloxone is preferred for unsupervised administration. The SUBOXONE sublingual film formulation contains buprenorphine with naloxone and is indicated for the treatment of opioid dependence, and may be used as initial treatment in patients physically dependent on heroin or other short-acting opioids and maintenance. Sublingual tablet formulations containing buprenorphine with naloxone are only indicated for the maintenance treatment of opioid dependence, meaning that they should be introduced after patients have initiated treatment with a buprenorphine-only product.

Buprenorphine alone is indicated for the treatment of opioid dependence and is preferred for use during induction for patients taking methadone or long-acting opioids (as per approved labeling). Additionally, buprenorphine-only products should be used in patients with severe hepatic impairment and in pregnant patients. Therefore, while you may see prescriptions for small amounts of buprenorphine alone for induction doses, and for some selected patients for whom the combination products are not recommended, you should expect the majority of prescriptions to be for buprenorphine with naloxone.

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

Full Prescribing Information for SUBOXONE sublingual film, SUBOXONE sublingual tablets, and SUBLTEX sublingual tablets can be found at www.IdiviorREMS.com.

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 3. Comparison of Available SUBOXONE Sublingual Film Strengths by Dimensions and Drug Concentrations

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

As part of the REMS, pharmacists dispensing SUBOXONE sublingual film, SUBOXONE sublingual tablets, or SUBUTEX sublingual tablets for opioid dependence must supply a Medication Guide with each prescription. The Medication Guide will be provided with the product and is also available by going online to www.IndiviorREMS.com or calling 1-877-782-6966.
What is the role of the pharmacist in ensuring safe use of buprenorphine-containing products?

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

> Verify that the prescription you receive is from a prescriber who is in compliance with the provisions of DATA 2000

> Keep in mind that a limited supply of buprenorphine-containing products should be dispensed during the initiation of therapy. This is due to the need of prescribers to closely and frequently assess the patients’ needs, their symptoms and potential risk of misuse, diversion, and abuse

> Provide the Medication Guide to patients each time the medicine is dispensed

> Remind patients who are picking up induction doses to return as directed to the doctor’s office so that they can be supervised while taking the medication

> Provide appropriate patient counseling on safe use of buprenorphine-containing products (see Section VI. Patient Information)

> Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

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 abusable?

Yes, buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when dispensing buprenorphine in situations when there is a concern about an increased risk of misuse, abuse or diversion. 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 pharmacist 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.

Pharmacists 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 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. 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, pharmacists 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.

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

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

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

Reference ID: 6822166
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.

Reference ID: 9822185
IV. Dispensing Prescriptions for Buprenorphine-Containing Products

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

Who is qualified to prescribe Buprenorphine-Containing Products?

A Federal law, Drug Addiction Treatment Act of 2000 (DATA 2000), limits office-based use of buprenorphine-containing products to prescribers who have met qualifications to receive a waiver. DEA issues the prescriber a unique identification number indicating that he or she is a qualifying prescriber under DATA 2000.

How can I verify that a prescription is legitimate?

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

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

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

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

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

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

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

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

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

Reference ID: 3822185
Are there confidentiality issues I should be aware of related to substance abuse treatment?

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

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

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

Under 42 CFR Part 2, before a prescriber can disclose any information to a third party about a patient’s treatment for substance abuse, that prescriber must first obtain the patient’s signed consent. The Federal Confidentiality disclosure restrictions discussed above (42 CFR Part 2.31) do not apply when it is the patient who delivers the prescription to the pharmacist, without direct communication from the prescriber to the pharmacist.

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

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

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

An example Consent Form is in the Appendix of this brochure.

To learn more about these regulations, visit the SAMHSA website, [http://www.samhsa.gov/healthprivacy/](http://www.samhsa.gov/healthprivacy/), or call 1-866-BUP-CSAT (1-866-286-2728).

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

SUBOXONE is a Schedule III controlled substance; therefore, buprenorphine-containing products are subject to certain federal regulations covering areas such as record keeping, inventory, proper dispensing and disposal. These are explained in the DEA’s Pharmacist’s Manual, which can be found at [www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html](http://www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html).

Many states have their own additional requirements for pharmacists dispensing controlled substances. Be sure to check with the appropriate authority in your state. For more information, visit the website of the National Association of Boards of Pharmacy at [www.nabp.net](http://www.nabp.net) for links to individual state boards of pharmacy.
V. Supplying and Administering Buprenorphine-Containing Products

How are buprenorphine-containing products supplied?

Table 4

<table>
<thead>
<tr>
<th>Product</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUBUTEX</strong>&lt;br&gt;(Buprenorphine sublingual tablets), including generic equivalents:</td>
<td>2 mg buprenorphine&lt;br&gt;8 mg buprenorphine</td>
</tr>
<tr>
<td><strong>SUBOXONE</strong>&lt;br&gt;(Buprenorphine and naloxone sublingual tablets), including generic equivalents:</td>
<td>2 mg buprenorphine / 0.5 mg naloxone&lt;br&gt;8 mg buprenorphine / 2 mg naloxone</td>
</tr>
<tr>
<td><strong>Zubsolv</strong>&lt;br&gt;(Buprenorphine and naloxone sublingual tablets):&lt;br&gt;Note: SUBOXONE film may also be administered by the buccal route.</td>
<td>1.4 mg buprenorphine / 0.36 mg naloxone&lt;br&gt;2.9 mg buprenorphine / 0.71 mg naloxone&lt;br&gt;5.7 mg buprenorphine / 1.4 mg naloxone&lt;br&gt;8.6 mg buprenorphine / 2.1 mg naloxone&lt;br&gt;11.4 mg buprenorphine / 2.9 mg naloxone</td>
</tr>
<tr>
<td><strong>SUBOXONE</strong>&lt;br&gt;(Buprenorphine and naloxone sublingual film):</td>
<td>2 mg buprenorphine / 0.5 mg naloxone&lt;br&gt;4 mg buprenorphine / 1 mg naloxone&lt;br&gt;8 mg buprenorphine / 2 mg naloxone&lt;br&gt;12 mg buprenorphine / 3 mg naloxone</td>
</tr>
<tr>
<td><strong>Bunavail</strong>&lt;br&gt;(Buprenorphine hydrochloride and naloxone hydrochloride buccal film)</td>
<td>2.1 mg buprenorphine / 0.3 mg naloxone&lt;br&gt;4.2 mg buprenorphine / 0.7 mg naloxone&lt;br&gt;6.3 mg buprenorphine / 1 mg naloxone</td>
</tr>
</tbody>
</table>

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.

Reference ID: 5822185
For Bunavail 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 Bunavail; open the Bunavail package immediately prior to use as indicated by the instructions; place the Bunavail film near the tip of a dry finger with the text facing up; place the side of the Bunavail film with the text against the inside of the cheek; press and hold the film in place for 5 seconds. Bunavail film(s) adhere to the moist buccal mucosa and should stay in place after this period.

If multiple films need to be administered, the patient should immediately apply the next film. Note that when two films are required for one dose, the patient should place one film on the inside of each cheek. For doses requiring multiple films, no more than two films should be applied to the inside of one cheek at a time. The patient should be instructed to avoid manipulating the film(s) with their tongue or finger(s) and should avoid drinking or eating food until the film(s) dissolve.

VI. Patient Information

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.

> 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.

Reference ID: 6822155
VII. 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)

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Reference ID: 3822195
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) __________________________

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.