

Initial REMS approval: 08/2010  
Most recent modification: 04/2014

**NDA 22-410**  
**SUBOXONE® (buprenorphine and naloxone) sublingual film CIII**  
**Buprenorphine (opioid partial agonist-antagonist)**  
**Naloxone (opioid antagonist)**

Reckitt Benckiser Pharmaceuticals Inc.  
10710 Midlothian Turnpike, Suite 430  
Richmond, VA 23235  
Telephone: 804-379-1090

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

*This REMS does not apply to SUBOXONE sublingual film dispensed to patients admitted to an Opioid Treatment Program (OTP) under 42 CFR Part 8 because the care of OTP patients is subject to specific requirements under those regulations.*

**I. GOAL(S):**

The goals of the REMS for SUBOXONE sublingual film are to:

- Mitigate the risks of accidental overdose, misuse and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with SUBOXONE sublingual film

**II. REMS ELEMENTS:**

**A. Medication Guide**

A Medication Guide will be dispensed with each SUBOXONE sublingual film prescription in accordance with 21 CFR 208.24.

The Medication Guides for buprenorphine-containing products are part of the SUBOXONE sublingual film REMS and will be provided with the product and is also available by going online to [www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.com) or calling 1-877-SUBOXONE (1-877-782-6966).

## B. Elements to Assure Safe Use

### 1. Safe use conditions

- a. SUBOXONE sublingual film will only be dispensed by the prescriber or prescribed to patients with documentation of the following safe use conditions:
  - i. Verification that the patient meets the diagnostic criteria for opioid dependence.
  - ii. Risks described in the professional labeling and the Medication Guide have been discussed with the patient.
  - iii. Safe storage of the medication has been explained and reviewed with the patient.
  - iv. After appropriate induction, the patient is prescribed a limited amount of medication at the first visit.
- b. Prescribers will document safe use conditions for each patient by using the [‘Appropriate Use Checklist,’](#) or by using another method (e.g. electronic health record) specific to the prescriber’s office practice.
- c. Reckitt Benckiser Pharmaceuticals Inc. will ensure that within 30 days of FDA approval of the SUBOXONE sublingual film REMS, a [Dear Prescriber Letter](#) will be mailed to all physicians certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This letter is designed to convey and reinforce the risks of accidental overdose, misuse, and abuse of SUBOXONE sublingual film, as well as the need to appropriately monitor patients and document safe use conditions. The prescriber brochure, [Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#), and the Appropriate Use Checklist will be appended to the Dear Prescriber Letter. The letter will provide instructions on where to obtain copies of the Full Prescribing Information and [Medication Guide](#). Mailings will occur annually thereafter.
- d. Reckitt Benckiser Pharmaceuticals Inc. will, on a monthly basis, identify any newly DATA 2000-certified physicians and mail the applicable documents to them. The prescriber brochure, [Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers](#) will be appended to the Prescriber Instruction Letter as well as the Medication Guide, Full Prescribing Information, and the Appropriate Use Checklist.
- e. To further reinforce safe use conditions, Reckitt Benckiser Pharmaceuticals Inc. will ensure that within 30 days of FDA approval of the SUBOXONE sublingual film REMS, a [Dear Pharmacist Letter](#) will be mailed to all pharmacists on a national mailing list of all retail pharmacies authorized by DEA to handle schedule 3 controlled substances on a national mailing list from the National Technical Information Service. The pharmacist brochure, [Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists](#) will be appended to the Dear Pharmacist Letter

as well as the Medication Guide, and Full Prescribing Information. Mailings will occur annually thereafter.

- f. Reckitt Benckiser Pharmaceuticals Inc. will make the letters and all materials that are appended to the letters available through its toll-free information line, through its field personnel, and on the SUBOXONE REMS website.

## **2. Monitoring**

- a. Each patient using SUBOXONE sublingual film will be subject to the following monitoring:
  - i. Return visits are scheduled at intervals commensurate with patient stability. Weekly, or more frequent, visits are recommended for the first month.
  - ii. Assessment and reinforcement of patient's compliance with the prescribed medication.
  - iii. Assessment of appropriateness of dosage prescribed.
  - iv. Assessment of whether patient is receiving the necessary psychosocial support.
  - v. Assessment of whether patient is making adequate progress towards treatment goals.
- b. Prescribers will document that each patient has received the required clinical monitoring using the 'Appropriate Use Checklist,' or by using another method/system (e.g. electronic health record) specific to the prescriber's office practice.

The following materials are part of the REMS and are appended to the REMS document:

- [SUBOXONE sublingual film Medication Guide](#)
- [Dear Prescriber Letter](#)
- [Dear Pharmacist Letter](#)
- [Appropriate Use Checklist](#)
- [Prescriber Brochure, "Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers"](#)
- [Pharmacist Brochure, "Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists"](#)
- SUBOXONE sublingual film REMS website ([www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.com))

## **C. Implementation System**

The Implementation System includes the following:

1. Reckitt Benckiser Pharmaceuticals Inc. will ensure that all DATA 2000-certified physicians receive the Dear Prescriber Letter with the appended materials.
2. Reckitt Benckiser Pharmaceuticals Inc. will monitor compliance with the requirements to document prescribing and dispensing with documentation of safe use conditions through surveys of patients and prescribers, evaluations of health care utilization databases, and ongoing surveillance (sources including, but not

- limited to, internet, street ethnography, national databases, and surveys conducted at substance abuse treatment programs).
3. Reckitt Benckiser Pharmaceuticals Inc. will monitor and evaluate the implementation of the elements to assure safe use provided for under [Sections B1](#), above, and in the manner described in the REMS supporting document, and will take reasonable steps to improve implementation of these elements to meet the goals of the REMS.

**D. Timetable for Submission of Assessments**

Reckitt Benckiser Pharmaceuticals Inc. will submit REMS Assessments to FDA at 6 months and at 12 months for the first year from the date of approval of the REMS, then annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Reckitt Benckiser Pharmaceuticals Inc. will submit each assessment so it will be received by the FDA on or before the due date.

**MEDICATION GUIDE**  
**SUBOXONE® (Sub-OX-own)**  
**(buprenorphine and naloxone)**  
**Sublingual Film (CIII)**

**IMPORTANT:**

Keep SUBOXONE in a secure place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally uses SUBOXONE, get emergency help right away.

Read this Medication Guide that comes with SUBOXONE before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor. Talk to your doctor or pharmacist if you have questions about SUBOXONE.

Share the important information in this Medication Guide with members of your household.

**What is the most important information I should know about SUBOXONE?**

- SUBOXONE can cause serious and life-threatening breathing problems. Call your doctor right away or get emergency help if:
  - You feel faint, dizzy, or confused
  - Your breathing gets much slower than is normal for youThese can be signs of an overdose or other serious problems.
- SUBOXONE contains an opioid that can cause physical dependence.
  - Do not stop taking SUBOXONE without talking to your doctor. You could become sick with uncomfortable withdrawal signs and symptoms because your body has become used to this medicine.
  - Physical dependence is not the same as drug addiction.
  - SUBOXONE is not for occasional or “as needed” use.
- An overdose and even death can happen if you take benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol while using SUBOXONE. Ask your doctor what you should do if you are taking one of these.
- Call a doctor or get emergency help right away if you:
  - Feel sleepy and uncoordinated
  - Have blurred vision
  - Have slurred speech
  - Cannot think well or clearly
  - Have slowed reflexes and breathing

- Do not inject (“shoot-up”) SUBOXONE
  - Injecting this medicine may cause life-threatening infections and other serious health problems.
  - Injecting SUBOXONE may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems, and cravings.
- In an emergency, have family members tell emergency department staff that you are physically dependent on an opioid and are being treated with SUBOXONE.

### **What is SUBOXONE?**

- SUBOXONE is a prescription medicine used to treat adults who are addicted to (dependent on) opioid drugs (either prescription or illegal) as part of a complete treatment program that also includes counseling and behavioral therapy.

SUBOXONE is a controlled substance (CIII) because it contains buprenorphine, which can be a target for people who abuse prescription medicines or street drugs. Keep your SUBOXONE in a safe place to protect it from theft. Never give your SUBOXONE to anyone else; it can cause death or otherwise harm them. Selling or giving away this medicine is against the law.

- It is not known if SUBOXONE is safe or effective in children.

### **Who should not take SUBOXONE?**

Do not take SUBOXONE if you are allergic to buprenorphine or naloxone.

### **What should I tell my doctor before taking SUBOXONE?**

**SUBOXONE may not be right for you. Before taking SUBOXONE, tell your doctor if you:**

- Have trouble breathing or lung problems
- Have an enlarged prostate gland (men)
- Have a head injury or brain problem
- Have problems urinating
- Have a curve in your spine that affects your breathing
- Have liver or kidney problems
- Have gallbladder problems
- Have adrenal gland problems
- Have Addison’s disease
- Have low thyroid (hypothyroidism)
- Have a history of alcoholism
- Have mental problems such as hallucinations (seeing or hearing things that are not there)
- Have any other medical condition
- Are pregnant or plan to become pregnant. It is not known if SUBOXONE will harm

your unborn baby. If you take SUBOXONE while pregnant, your baby may have symptoms of withdrawal at birth. Talk to your doctor if you are pregnant or plan to become pregnant.

- Are breast feeding or plan to breast feed. SUBOXONE can pass into your milk and may harm your baby. Talk to your doctor about the best way to feed your baby if you take SUBOXONE. Monitor your baby for increased sleepiness and breathing problems.

**Tell your doctor about all the medicines you take**, including prescription and nonprescription medicines, vitamins, and herbal supplements. SUBOXONE may affect the way other medicines work, and other medicines may affect how SUBOXONE works. Some medicines may cause serious or life-threatening medical problems when taken with SUBOXONE.

Sometimes the doses of certain medicines and SUBOXONE may need to be changed if used together. Do not take any medicine while using SUBOXONE until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines while you are using SUBOXONE.

**Be especially careful about taking other medicines that may make you sleepy**, such as pain medicines, tranquilizers, antidepressant medicines, sleeping pills, anxiety medicines or antihistamines.

Know the medicines you take. Keep a list of them to show your doctor or pharmacist each time you get a new medicine.

#### **How should I take SUBOXONE sublingual film?**

- Always take SUBOXONE exactly as your doctor tells you. Your doctor may change your dose after seeing how it affects you. Do not change your dose unless your doctor tells you to change it.
- Do not take SUBOXONE more often than prescribed by your doctor.
- Each SUBOXONE sublingual film comes in a sealed child-resistant foil pouch. Wait to open SUBOXONE until right before you use it.
- To open your SUBOXONE sublingual film foil pouch, fold along the dotted line (see Figure 1)



Figure 1

- Tear down at slit or cut with scissors along the arrow (see Figure 2).



Figure 2

- Before taking SUBOXONE, drink water to moisten your mouth. This helps the film dissolve more easily.
- Hold the film between two fingers by the outside edges.
- **Place SUBOXONE sublingual film under your tongue**, close to the base either to the left or right of the center (see Figure 3).





Figure 3

- If your doctor tells you to take 2 films at a time, place the second film under your tongue on the opposite side. Try to avoid having the films touch as much as possible.
- Keep the films in place until they have completely dissolved.
- If you are directed to take a third film, place it under your tongue on either side after the first 2 films have dissolved.
- While SUBOXONE is dissolving, do not chew or swallow the film because the medicine will not work as well.
- Talking while the film is dissolving can affect how well the medicine in SUBOXONE is absorbed.
- If you miss a dose of SUBOXONE, take your medicine when you remember. If it is almost time for your next dose, skip the missed dose and take the next dose at your regular time. Do not take 2 doses at the same time unless your doctor tells you to. If you are not sure about your dosing, call your doctor.
- Do not stop taking SUBOXONE suddenly. You could become sick and have withdrawal symptoms because your body has become used to the medicine. Physical dependence is not the same as drug addiction. Your doctor can tell you more about the differences between physical dependence and drug addiction. To have fewer withdrawal symptoms, ask your doctor how to stop using SUBOXONE the right way.
- **If you take too much SUBOXONE or overdose, call Poison Control or get emergency medical help right away.**

#### What should I avoid while taking SUBOXONE?

- **Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how this medication affects you.** Buprenorphine can cause drowsiness and slow reaction times. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative drugs when you take SUBOXONE.

- **You should not drink alcohol** while using SUBOXONE, as this can lead to loss of consciousness or even death.

#### **What are the possible side effects of SUBOXONE?**

##### **SUBOXONE can cause serious side effects, including:**

- **See “What is the most important information I should know about SUBOXONE?”**
- **Respiratory problems.** You have a higher risk of death and coma if you take SUBOXONE with other medicines, such as benzodiazepines.
- **Sleepiness, dizziness, and problems with coordination**
- **Dependency or abuse**
- **Liver problems.** Call your doctor right away if you notice any of these signs of liver problems: Your skin or the white part of your eyes turning yellow (jaundice), urine turning dark, stools turning light in color, you have less of an appetite, or you have stomach (abdominal) pain or nausea. Your doctor should do tests before you start taking and while you take SUBOXONE.
- **Allergic reaction.** You may have a rash, hives, swelling of the face, wheezing, or a loss of blood pressure and consciousness. Call a doctor or get emergency help right away.
- **Opioid withdrawal.** This can include: shaking, sweating more than normal, feeling hot or cold more than normal, runny nose, watery eyes, goose bumps, diarrhea, vomiting, and muscle aches. Tell your doctor if you develop any of these symptoms.
- **Decrease in blood pressure.** You may feel dizzy if you get up too fast from sitting or lying down.

##### **Common side effects of SUBOXONE sublingual film include:**

- Nausea
- Vomiting
- Drug withdrawal syndrome
- Headache
- Sweating
- Numb mouth
- Constipation
- Painful tongue
- The inside of your mouth is more red than normal
- Intoxication (feeling lightheaded or drunk)
- Disturbance in attention
- Irregular heart beat (palpitations)
- Decrease in sleep (insomnia)
- Blurred vision
- Back pain
- Fainting
- Dizziness
- Sleepiness

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects of SUBOXONE sublingual film. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store SUBOXONE?**

- Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).
- **Keep SUBOXONE in a safe place, out of the sight and reach of children.**

#### **How should I dispose of unused SUBOXONE sublingual film?**

- Dispose of unused SUBOXONE as soon as you no longer need them.
- Unused films should be removed from the foil pouch and flushed down the toilet.

#### **General information about the safe and effective use of SUBOXONE**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take SUBOXONE for a condition for which it was not prescribed. Do not give SUBOXONE to other people, even if they have the same symptoms you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about SUBOXONE. If you would like more information, talk to your doctor or pharmacist. You can ask your doctor or pharmacist for information that is written for healthcare professionals. For more information call 1-877-782-6966.

#### **What are the ingredients in SUBOXONE sublingual film?**

**Active Ingredients:** buprenorphine and naloxone.

**Inactive Ingredients:** polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

Manufactured for Reckitt Benckiser Pharmaceuticals Inc.  
Richmond, VA 23235 by MonoSol Rx LLC, Warren, NJ 07059

This Medication Guide has been approved by the US Food and Drug Administration.

SUBOXONE® is a registered trademark of Reckitt Benckiser Healthcare (UK) Ltd.

April 2014

Copyright © 2014 Reckitt Benckiser Pharmaceuticals Inc.

Printed in USA

## IMPORTANT DRUG WARNING

**Subject: Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE® and SUBUTEX® for opioid dependence due to risks of accidental overdose, misuse, and abuse.**

<DATE>

Dear Prescriber:

You are receiving this letter because you are a prescriber certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000).

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE, SUBUTEX and the generic equivalent products. This REMS does not apply to SUBOXONE or SUBUTEX products that are dispensed to patients in an Opioid Treatment Program (OTP) under 42 CFR Part 8 because the care of OTP patients is subject to specific requirements under those regulations.

The FDA has determined that a REMS is necessary to ensure that the benefits of SUBOXONE and SUBUTEX products for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Please be aware that:

- SUBOXONE sublingual film is indicated for the induction of patients physically dependent on heroin or other short-acting opioids and maintenance treatment of opioid dependence.
- SUBUTEX buprenorphine-only sublingual tablets and generic equivalents are indicated for the treatment of opioid dependence.
- Patients physically dependent on heroin or other short-acting opioids may initiate treatment with either SUBOXONE sublingual film or with a buprenorphine-only sublingual product. SUBOXONE sublingual film is preferred over buprenorphine-only products for unsupervised administration.
- SUBUTEX and generic equivalent buprenorphine-only tablets are preferred for induction for patients physically dependent on methadone or long-acting opioids taken as per approved labeling.
- SUBOXONE sublingual tablets, including generic equivalents and Zubsolv sublingual tablets are indicated for the maintenance treatment of opioid dependence after initial induction.
- All of these products are used as part of a complete treatment plan, including counseling and/or psychosocial support.

### **Serious Risks of SUBOXONE and SUBUTEX**

Please communicate the following key messages to patients about the risks of accidental overdose, misuse, and abuse while taking SUBOXONE and SUBUTEX products:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) with these products. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.
- Instruct patients to keep these products in a secure place and out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed to one of these products, medical attention should be sought immediately.
- Advise patients that these products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Caution patients to keep their medication in a safe place, and to protect it from theft.
- Instruct patients never to give these products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away these products is against the law.

### **Prescriber Action**

You are encouraged to read the enclosed educational brochure entitled ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers***. Under the SUBOXONE REMS program, prescribers are strongly encouraged to perform and document all of the following actions:

- Verify the patient meets diagnostic criteria for opioid dependence
- Discuss the risks associated with these products, 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 that will last until the next visit
- Explain how to safely store the medication out of reach of children
- Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month)
- Consider “film count”/dose reconciliation
- Assess whether the patient is receiving the counseling/psychosocial support considered necessary for treatment
- Assess whether the patient is making progress toward treatment goals, including, as appropriate, urine toxicology testing
- Continually assess appropriateness of maintenance dose
- Continually assess benefits of treatment outweigh the risks

### **Patient Monitoring and Appropriate Dosing Info**

An ***Appropriate Use Checklist*** is enclosed to assist you in performing and documenting the

above prescriber actions of the SUBOXONE REMS. You may use the enclosed checklist or other means (e.g., electronic health record) specific to your office practice to document that the above actions have been completed for each patient.

### **Medication Guide**

The SUBOXONE REMS and SUBUTEX REMS include product specific Medication Guides on the safe and effective use of SUBOXONE and SUBUTEX. A Medication Guide will be dispensed with each prescription of SUBOXONE and SUBUTEX. Please review this important information with your patients or their caregivers. Please also discuss the importance of participating in a complete treatment program that may include counseling, behavioral therapy, and/or psychosocial support.

### **Reporting Adverse Events**

To report SUSPECTED ADVERSE EVENTS contact:

- Reckitt Benckiser Pharmaceuticals Inc. at 1-877-SUBOXONE (1-877-782-6966) or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This letter is not a comprehensive description of the risks associated with the use of SUBOXONE and SUBUTEX. Additional important safety information can be found in the ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers*** educational brochure and Full Prescribing Information.

Additional copies of the educational brochure, Appropriate Use Checklist, Full Prescribing Information, and Medication Guide for each product covered under the SUBOXONE REMS and SUBUTEX REMS, can be obtained at [www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.com), <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> or by contacting the toll-free call center at 1-877-782-6966.

Sincerely,

<NAME>

<TITLE>

Reckitt Benckiser Pharmaceuticals Inc.

*Enclosures:* Appropriate Use Checklist  
Prescriber Brochure: *"Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers"*  
SUBOXONE sublingual film Medication Guide  
SUBOXONE sublingual film Full Prescribing Information

April 2014

## IMPORTANT DRUG WARNING

**Subject: Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE® and SUBUTEX® for opioid dependence due to risks of accidental overdose, misuse, and abuse.**

<DATE>

Dear Pharmacist:

The purpose of this letter is to inform you of a Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE, SUBUTEX and the generic equivalent products. This REMS does not apply to SUBOXONE or SUBUTEX products that are dispensed to patients in an Opioid Treatment Program (OTP) under 42 CFR Part 8 because the care of OTP patients is subject to specific requirements under those regulations.

The FDA has determined that a REMS is necessary to ensure that the benefits of SUBOXONE and SUBUTEX products for opioid dependence outweigh the potential risks of accidental overdose, misuse, and abuse. Please be aware that:

- SUBOXONE sublingual film is indicated for the induction of patients physically dependent on heroin or other short-acting opioids and maintenance treatment of opioid dependence.
- SUBUTEX buprenorphine-only sublingual tablets and generic equivalents are indicated for the treatment of opioid dependence.
- Patients physically dependent on heroin or other short-acting opioids may initiate treatment with either SUBOXONE sublingual film or with a buprenorphine-only sublingual product. SUBOXONE sublingual film is preferred over buprenorphine-only products for unsupervised administration.
- SUBUTEX and generic equivalent buprenorphine-only tablets are preferred for induction for patients physically dependent on methadone or long-acting opioids taken as per approved labeling.
- SUBOXONE sublingual tablets, including generic equivalents and Zubsolv sublingual tablets are indicated for the maintenance treatment of opioid dependence after initial induction.
- All of these products are used as part of a complete treatment plan, including counseling and/or psychosocial support.

### **Serious Risks of SUBOXONE and SUBUTEX**

Please communicate the following key messages to patients about the risks of accidental overdose, misuse, and abuse while taking SUBOXONE and SUBUTEX products:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) with these products. Caution patients prescribed benzodiazepines or other CNS depressants to use them only as directed by their prescriber.

- Instruct patients to keep these products in a secure place and out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed to one of these products, medical attention should be sought immediately.
- Advise patients that these products contain an opioid that can be a target for people who abuse prescription medications or street drugs. Caution patients to keep their medication in a safe place, and to protect it from theft.
- Instruct patients never to give these products to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away these products is against the law.

### **Pharmacist Action**

You are encouraged to read the enclosed educational brochure entitled ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists***. Each time you fill a prescription for SUBOXONE or SUBUTEX, 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 SUBOXONE or SUBUTEX 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 the safe use of SUBOXONE and SUBUTEX
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

### **Medication Guide**

The SUBOXONE REMS and SUBUTEX REMS include product specific Medication Guides on the safe and effective use of SUBOXONE and SUBUTEX. Provide a Medication Guide to your patients or their caregivers with each dispensing and encourage them to read it. Please also promote the importance of participating in a complete treatment program that may include counseling, behavioral therapy, and/or psychosocial support.

### **Reporting Adverse Events**

To report SUSPECTED ADVERSE EVENTS contact:

- Reckitt Benckiser Pharmaceuticals Inc. at 1-877-SUBOXONE (1-877-782-6966) or



- FDA MedWatch program by phone at 1-800-FDA-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This letter is not a comprehensive description of the risks associated with the use of SUBOXONE and SUBUTEX. Additional important safety information can be found in the ***Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*** educational brochure and Full Prescribing Information.

Additional copies of the educational brochure, Full Prescribing Information, and Medication Guide for each product covered under the SUBOXONE REMS and SUBUTEX REMS, can be obtained at [www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.com), <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> or by contacting the toll-free call center at 1-877-782-6966.

Sincerely,

<NAME>

<TITLE>

Reckitt Benckiser Pharmaceuticals Inc.

*Enclosures:* SUBOXONE Film Medication Guide  
Pharmacist Brochure: *Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists*  
SUBOXONE Film Full Prescribing Information

April 2014

## **SUBOXONE<sup>®</sup> APPROPRIATE USE CHECKLIST:**

This checklist is a useful reminder of the safe use conditions and monitoring requirements for prescribing SUBOXONE (buprenorphine and naloxone) CIII products for opioid dependence.

SUBOXONE sublingual film is indicated for the induction of patients physically dependent on heroin or other short-acting opioids and maintenance treatment of opioid dependence.

Requirements to address during each patient's appointment include:

- understanding and reinforcement of safe use conditions
- the importance of psychosocial counseling
- screening and monitoring patients to determine progress towards treatment goals

If a patient continues to abuse various drugs or is unresponsive to treatment, including psychosocial intervention, it is important that you assess the need to refer the patient to a specialist and/or a more intensive behavioral treatment environment.

Additional resource: Physician Clinical Support System: [www.pcssmat.org](http://www.pcssmat.org)

**This checklist may be used during the induction period and filed in patient's medical record to document safe use conditions. Once a maintenance dose has been established, use the maintenance checklist.**

Measurement to Ensure Appropriate Use	NOTES:
Date:	
Induction	
<input type="checkbox"/> Verified patient meets diagnostic criteria for opioid dependence	
<input type="checkbox"/> Discussed risks described in professional labeling and Medication Guide with patient	
<input type="checkbox"/> Explained or reviewed conditions of safe storage of medication	
<input type="checkbox"/> Provided induction doses under appropriate supervision	

<input type="checkbox"/> Prescribed limited amount of medication at first visit	
<input type="checkbox"/> Scheduled next visit at interval commensurate with patient stability <ul style="list-style-type: none"> <li>• Weekly or more frequent visits recommended for the first month</li> </ul>	

**This checklist may be used for visits following the induction period and filed in patient's medical record to document safe use conditions.**

<b>Measurement to Ensure Appropriate Use</b>	<b>NOTES:</b>
<b>Date:</b>	
<b>Visit #:</b>	
<b>Maintenance</b>	
<input type="checkbox"/> Assessed and encouraged patient to take medication as prescribed <ul style="list-style-type: none"> <li>• Consider film count/dose reconciliation</li> </ul>	
<input type="checkbox"/> Assessed appropriateness of dosage <ul style="list-style-type: none"> <li>• SUBOXONE 16 mg/4 mg is recommended for maintenance</li> <li>• Doses higher than this should be an exception</li> <li>• The need for higher dose should be carefully evaluated</li> </ul>	
<input type="checkbox"/> Conduct urine drug screens as appropriate to assess use of illicit substances	
<input type="checkbox"/> Assessed participation in professional counseling and support services	
<input type="checkbox"/> Assessed whether benefits of treatment with buprenorphine-containing products outweigh risks associated with SUBOXONE	

<p>☐ Assessed whether patient is making adequate progress toward treatment goals</p> <ul style="list-style-type: none"> <li>• Considered results of urine drug screens as part of the evidence of the patient complying with the treatment program</li> <li>• Consider referral to more intensive forms of treatment for patients not making progress</li> </ul>	
<p>☐ Scheduled next visit at interval commensurate with patient stability</p> <ul style="list-style-type: none"> <li>• Weekly, or more frequent visits are recommended for the first month</li> </ul>	

SUBOXONE (buprenorphine and naloxone) sublingual film CIII  
SUBOXONE® is a registered trademark of Reckitt Benckiser Healthcare (UK) Ltd.

Copyright © 2014 Reckitt Benckiser Pharmaceuticals Inc.  
April 2014  
Printed in USA

# Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Prescribers

SUBOXONE<sup>®</sup>

(buprenorphine and naloxone) sublingual film CIII

### III. I. INTRODUCTION

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) for prescribers of SUBOXONE<sup>®</sup> (buprenorphine and naloxone) sublingual film CIII who are certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000). This REMS does not apply to SUBOXONE sublingual film that is 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 SUBOXONE sublingual film, a buprenorphine-containing product.

#### **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 SUBOXONE sublingual film* 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**

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 5.7 mg buprenorphine / 1.4 mg naloxone
SUBOXONE sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone

### Indications:

SUBUTEX® (buprenorphine) sublingual tablets CIII and generic equivalents are indicated for the treatment of opioid dependence and are preferred for induction.

SUBOXONE sublingual tablets, including generic equivalents and Zubsolv sublingual tablets are indicated for the maintenance treatment of opioid dependence after initial 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 patients physically dependent on methadone or long-acting opioids taken as per approved labeling. Patients being switched between different formulations should be started on the corresponding dose (as shown in Table 2 below) compared to the previously administered product. Patients should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated<sup>1</sup>.

**Table 2**

Corresponding doses of buprenorphine products that contain naloxone		
SUBOXONE tablets Buprenorphine and naloxone sublingual tablets, including generic equivalents	SUBOXONE sublingual film	Zubsolv sublingual tablets
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone

<sup>1</sup> 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.

Corresponding doses of buprenorphine products that contain naloxone		
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone

**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

SUBOXONE sublingual film unit strength (buprenorphine/naloxone)	SUBOXONE sublingual film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53



4 mg/1 mg  (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg  (1.5 times the length of the 8 mg/2 mg unit)	22.0 mm x 19.2 mm	17.2	4.88

#### IV. 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?**

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with SUBOXONE sublingual film outweigh the potential risks.

The goals of the REMS for SUBOXONE sublingual film 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

##### **What is my role with regard to the SUBOXONE sublingual film REMS?**

To meet the requirements of the REMS and to ensure the benefits of prescribing SUBOXONE sublingual film 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 “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 REMS, prescribers of SUBOXONE sublingual film 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.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.com) or by calling 1-877-782-6966.

## V. III. HIGHLIGHTED IMPORTANT SAFETY INFORMATION FOR SUBOXONE

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

### A. ABUSE POTENTIAL OF SUBOXONE

#### Is SUBOXONE abusable?

Yes, buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing 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 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, SUBOXONE can 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, 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 SUBOXONE cause dependence?**

Yes, buprenorphine, the active ingredient in SUBOXONE 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 about withdrawal symptoms?**

If a dependent patient abruptly discontinues use of buprenorphine, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it is appropriate to taper the buprenorphine dose, rather than abruptly discontinue the medication. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

#### **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 SUBOXONE. When determining the quantity of SUBOXONE 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 SUBOXONE in children?**

Patients should be instructed to keep SUBOXONE 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 SUBOXONE, seek immediate urgent medical attention.

## **What is an appropriate medical response to an overdose of SUBOXONE?**

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.

### **B. CONTRAINDICATIONS**

- Hypersensitivity to buprenorphine or naloxone

### **C. 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, SUBOXONE, or both in situations of concomitant prescription
- Store SUBOXONE 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 SUBOXONE to patients with known hypersensitivity to buprenorphine or naloxone
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of SUBOXONE 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
- SUBOXONE is 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
- Buprenorphine/naloxone drug products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Buprenorphine/naloxone drug products are not recommended for induction in

patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. However, SUBOXONE sublingual film may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone.

### ***Adverse Reactions***

#### **What are the commonly observed adverse events of SUBOXONE sublingual film and SUBOXONE sublingual tablet?**

- Adverse events commonly observed with the sublingual 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 tablet are: 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.
- To report SUSPECTED ADVERSE REACTIONS contact:
  - Reckitt Benckiser Pharmaceuticals Inc. at 1-877-SUBOXONE (1-877-782-6966) or
  - FDA MedWatch program by phone at 1-800-FDA-1088, or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

### **D. DRUG INTERACTIONS**

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

### **E. USE IN SPECIFIC POPULATIONS**

- Pregnancy: Based on animal data, buprenorphine (the active ingredient in SUBOXONE) may cause fetal harm
- Nursing mothers: Caution should be exercised when SUBOXONE is administered to a nursing woman
- Safety and effectiveness of SUBOXONE in patients below the age of 16 has not been established
- Administer SUBOXONE with caution to elderly or debilitated patients
- SUBOXONE sublingual film is not recommended for use in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment

## IV. Prescribing SUBOXONE sublingual film

### When should SUBOXONE sublingual film be prescribed?

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

### What is the proper protocol for induction with SUBOXONE sublingual film?

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.

#### *Patients taking methadone or long-acting opioids:*

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

To avoid precipitating a withdrawal syndrome, induction should be undertaken when objective signs of moderate withdrawal are evident. A clinical tool (e.g., Clinical Opiate Withdrawal Scale (COWs) score > 12) to assess withdrawal should be used.

#### *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 with 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.

In some studies, gradual induction over several days led to a high rate of drop-out during the induction period. Therefore, it is recommended that an adequate maintenance dose, titrated to clinical effectiveness, be achieved as rapidly as possible to prevent undue opioid withdrawal signs and symptoms.

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.

### How should patients be maintained with SUBOXONE sublingual film?

After treatment induction and stabilization, the maintenance dosage of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg to 24 mg/6 mg per day depending on the

patient's clinical response. The dosage of SUBOXONE sublingual film should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

The recommended target dosage of SUBOXONE sublingual film during maintenance is 16 mg/4 mg per day as a single daily dose. Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage.

### **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 SUBOXONE 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. SUBOXONE 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 SUBOXONE 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 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 SUBOXONE sublingual film in their offices, it is important to develop a good working relationship with your local pharmacies. To ensure that you will be able to exchange information with the pharmacist, such as confirming the validity of your induction prescriptions, it is recommended that you have the patient sign a release of information at the time of the initial office visit. A sample consent form with all the elements required under 42 CFR Part 2.31 is included in Appendix A of this brochure with this booklet (see page *(insert page number after formatted)*.



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 SUBOXONE sublingual film will be valid at any pharmacy authorized by DEA to handle schedule III controlled substances. However, prior to prescribing SUBOXONE sublingual film 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 SUBOXONE?**

If you wish to maintain a supply of SUBOXONE sublingual film 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 SUBOXONE 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 SUBOXONE 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 18). It is particularly important to obtain the patient's consent if you elect to phone or fax in prescriptions, as this constitutes disclosure of the patient's treatment. When the prescription is directly transmitted by the prescriber, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42 CFR Part 2.31 does not apply when it is the patient who delivers the prescription to the pharmacist, without direct communication from the prescriber to the pharmacist.

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

## **F. DOSING AND ADMINISTRATION OF SUBOXONE SUBLINGUAL FILM**

### **How do I maintain clinically effective dosing for stabilized patients?**

The recommended target dose is 16 mg buprenorphine/4 mg naloxone per day. Clinical studies have shown that this is a clinically effective dose. Although lower doses may be effective in some patients, for most patients, a 16 mg 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 24mg/6mg buprenorphine/naloxone per day for SUBOXONE. The reported lack of significant increase in brain mu-receptor occupancy between doses of 16 mg and 32 mg implies that there should be little difference in clinical effectiveness at doses between 16 mg and 24 mg in most patients. 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 3**

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 5.7 mg buprenorphine / 1.4 mg naloxone
SUBOXONE sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone

### **How should SUBOXONE sublingual film be administered?**

Have the patient to place the SUBOXONE sublingual film under the tongue. If an additional film is necessary to achieve the prescribed dose, the additional film should be placed sublingually on the opposite side from the first film. If an additional third film is needed, place it sublingually after the first 2 SUBOXONE sublingual films have dissolved. Place SUBOXONE sublingual films in a manner to minimize overlapping as much as possible. Keep the films under the tongue, close to the base on the left or right side, until they are completely dissolved. SUBOXONE sublingual film should NOT be chewed, swallowed, or moved after placement. Swallowing the film reduces the bioavailability of the drug.

### **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.

#### **G. DISCONTINUING THERAPY WITH SUBOXONE**

##### **What can I tell patients who wish to discontinue treatment?**

Patients should be advised not to change the dose of SUBOXONE without consulting their prescriber. Patients seeking to discontinue treatment with SUBOXONE 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 SUBOXONE, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the dose of SUBOXONE, rather than abruptly discontinue it. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

### **VI. 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 SUBOXONE 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 SUBOXONE 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 SUBOXONE, urgent medical attention should be sought immediately

- Advise patients that SUBOXONE contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their SUBOXONE in a safe place and to protect them from theft
- Instruct patients never to give SUBOXONE 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 SUBOXONE is against the law
- Caution patients that SUBOXONE 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 SUBOXONE without consulting their prescriber
- After treatment induction, advise patients to take SUBOXONE once a day as directed
- Inform patients that SUBOXONE 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 SUBOXONE 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, SUBOXONE 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 SUBOXONE during pregnancy
- Advise nursing mothers treated with SUBOXONE 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 SUBOXONE
- 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.

## **VII. VI. WHERE CAN I GET MORE INFORMATION ON TREATING PATIENTS WITH SUBOXONE SUBLINGUAL FILM?**

Refer to the package insert for Full Prescribing Information which can be found at [www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.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](http://www.asam.org))
- American Academy of Addiction Psychiatry website ([www.aaap.org](http://www.aaap.org))
- Physician Clinical Support System - Buprenorphine ([www.pcssmat.org](http://www.pcssmat.org))

SUBOXONE<sup>®</sup> is a registered trademark of Reckitt Benckiser Healthcare (UK) Ltd.

## 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.

Manufactured for Reckitt Benckiser Pharmaceuticals Inc.

Richmond, VA 23235 by MonoSol Rx LLC, Warren, NJ 07059

Copyright © 2014 Reckitt Benckiser Pharmaceuticals Inc.

April 2014

Printed in USA



# Office-Based Buprenorphine Therapy for Opioid Dependence: Important Information for Pharmacists

SUBOXONE<sup>®</sup>

(buprenorphine and naloxone) sublingual film CIII

## 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 and the important safety issues and messages needed to counsel patients about its safe use. This REMS does not apply to SUBOXONE sublingual film that is 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**

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 5.7 mg buprenorphine / 1.4 mg naloxone
SUBOXONE sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone

### Indications:

SUBUTEX® (buprenorphine) sublingual tablets CIII and generic equivalents are indicated for the treatment of opioid dependence and are preferred for induction.

SUBOXONE sublingual tablets, including generic equivalents and Zubsolv sublingual tablets are indicated for the maintenance treatment of opioid dependence after initial 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 patients physically dependent on methadone or long-acting opioids taken as per approved labeling. Patients being switched between different formulations should be started on the corresponding dose (as shown in Table 2 below) compared to the previously administered product. Patients should be monitored for symptoms related to over-dosing or under-dosing and dosing adjustments should be made as clinically indicated<sup>2</sup>.

**Table 2**

<b>Corresponding doses of buprenorphine products that contain naloxone</b>		
SUBOXONE tablets Buprenorphine and naloxone sublingual tablets, including generic equivalents	SUBOXONE sublingual film	Zubsolv sublingual tablets
2 mg buprenorphine/ 0.5 mg naloxone	2 mg buprenorphine/ 0.5 mg naloxone	1.4 mg buprenorphine/ 0.36 mg naloxone
8 mg buprenorphine/ 2 mg naloxone	8 mg buprenorphine/ 2 mg naloxone	5.7 mg buprenorphine/ 1.4 mg naloxone

### **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, including induction in patients physically dependent on heroin or other short-acting opioids and maintenance. Sublingual tablet formulations

<sup>2</sup> 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 and Zubsolv tablets. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to films or vice-versa.

containing buprenorphine with naloxone are only indicated for the maintenance treatment of opioid dependence.

Buprenorphine alone is indicated for the treatment of opioid dependence and is preferred for use during induction. Buprenorphine-only tablets are preferred for patients taking methadone or long-acting opioids (as per approved labeling). Therefore, while you may see prescriptions for small amounts of buprenorphine alone for induction doses, you should expect the majority of prescriptions to be for buprenorphine with naloxone.

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

Full Prescribing Information for SUBUTEX and SUBOXONE products can be found at [www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.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

SUBOXONE sublingual film unit strength (buprenorphine/naloxone)	SUBOXONE sublingual film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
---	--	-------------------------------------	--------------------------------

2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg  (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg  (1.5 times the length of the 8 mg/2 mg unit)	22.0 mm x 19.2 mm	17.2	4.88

## 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?

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with SUBOXONE sublingual film outweigh the potential risks.

The goals of the REMS for SUBOXONE sublingual film 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

### What is my role with regard to the SUBOXONE sublingual film REMS?

As part of the REMS, pharmacists dispensing SUBOXONE sublingual film for opioid dependence must supply a Medication Guide for SUBOXONE sublingual film with each prescription. The Medication Guide will be provided with the product and is also available by going online to [www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.com) or calling 1-877-SUBOXONE (1-877-782-6966).

### What is the role of the pharmacist in ensuring safe use of SUBOXONE?

As a pharmacist, you will play an important role in ensuring that SUBOXONE is used safely and appropriately. Each time you fill a prescription for SUBOXONE, 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 SUBOXONE 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 SUBOXONE (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 SUBOXONE**

This section of the brochure highlights important safety information to consider when dispensing SUBOXONE **Please refer to the Full Prescribing Information (FPI) for detailed safety-related information for SUBOXONE.**

#### ***Abuse Potential of SUBOXONE***

##### **Is SUBOXONE 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, SUBOXONE can 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, 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 SUBOXONE cause dependence?**

Yes, buprenorphine, the active ingredient in SUBOXONE, 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.

### **What about withdrawal symptoms?**

If a dependent patient abruptly discontinues use of buprenorphine, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it is appropriate to taper the buprenorphine dose, rather than abruptly discontinue the medication. The prescriber can provide a dose schedule to accomplish a gradual discontinuation of the medication.

### **How can patients prevent accidental exposure to SUBOXONE in children?**

Patients should be instructed to keep SUBOXONE 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 SUBOXONE, seek immediate urgent medical attention.

### **What is an appropriate medical response to an overdose of SUBOXONE?**

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

### ***Contraindications***

- Hypersensitivity to buprenorphine 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, SUBOXONE, or both in situations of concomitant prescription
- Store SUBOXONE 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 SUBOXONE to patients with known hypersensitivity to buprenorphine or naloxone
- An opioid withdrawal syndrome is likely to occur with parenteral misuse of SUBOXONE 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
- SUBOXONE is 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
- Buprenorphine/naloxone drug products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. Buprenorphine/naloxone drug products are not recommended for induction in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. However, SUBOXONE sublingual film may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone.

### ***Adverse Reactions***

#### **What are the commonly observed adverse events of SUBOXONE sublingual film and SUBOXONE sublingual tablet?**

- Adverse events commonly observed with the sublingual 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 tablet are: 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.

- To report SUSPECTED ADVERSE REACTIONS contact:
  - Reckitt Benckiser Pharmaceuticals Inc. at 1-877-SUBOXONE (1-877-782-6966) or
  - FDA MedWatch program by phone at 1-800-FDA-1088, or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

### ***Drug Interactions***

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

### ***Use in Specific Populations***

- Pregnancy: Based on animal data, buprenorphine (the active ingredient in SUBOXONE) may cause fetal harm
- Nursing mothers: Caution should be exercised when SUBOXONE is administered to a nursing woman
- Safety and effectiveness of SUBOXONE in patients below the age of 16 has not been established
- Administer SUBOXONE with caution to elderly or debilitated patients
- SUBOXONE sublingual film is not recommended for use in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment

## **IV. Dispensing Prescriptions for SUBOXONE**

This section discusses important information to consider before filling prescriptions for SUBOXONE.

### **Who is qualified to prescribe SUBOXONE?**

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 be sure a prescriber is qualified to prescribe SUBOXONE?**

Pharmacists can verify the validity of a prescriber's DATA 2000 waiver by calling 1-866-BUP-CSAT (1-866-287-2728), or e-mailing [info@buprenorphine.samhsa.gov](mailto:info@buprenorphine.samhsa.gov).

DEA regulations require the prescriber's unique identification number, along with the existing DEA registration number, be included on all prescriptions for buprenorphine-containing products for the treatment of opioid dependence.

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

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

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

**How can I verify that a prescription is legitimate?**

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

However, even if you determine that an individual prescription is legitimate, you should still be aware of other means by which patients may attempt to divert their prescriptions. For example, an opioid user may present themselves to two or more qualified prescribers and therefore, receive multiple prescriptions for SUBOXONE or other 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](mailto:info@buprenorphine.samhsa.gov); DEA ([www.deadiversion.usdoj.gov](http://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](http://www.fsmb.org/directory_smb.html)).

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

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

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

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

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

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

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

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

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

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

### **Are there any special storage, record keeping, or other requirements associated with SUBOXONE?**

SUBOXONE is a schedule III controlled substance; therefore, SUBOXONE is 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?**

SUBUTEX (Buprenorphine sublingual tablets), including generic equivalents:	2 mg buprenorphine 8 mg buprenorphine
--	--

SUBOXONE (Buprenorphine and naloxone sublingual tablets), including Suboxone and 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 5.7 mg buprenorphine / 1.4 mg naloxone
SUBOXONE sublingual film (Buprenorphine and naloxone sublingual film):	2 mg buprenorphine / 0.5 mg naloxone 4 mg buprenorphine / 1 mg naloxone 8 mg buprenorphine / 2 mg naloxone 12 mg buprenorphine / 3 mg naloxone

#### **How should SUBOXONE sublingual film be administered?**

Have the patient to place the SUBOXONE sublingual film under the tongue. If an additional film is necessary to achieve the prescribed dose, the additional film should be placed sublingually on the opposite side from the first film. If an additional third film is needed, place it sublingually after the first 2 SUBOXONE sublingual films have dissolved. Place SUBOXONE sublingual films in a manner to minimize overlapping as much as possible. Keep the films under the tongue, close to the base on the left or right side, until they are completely dissolved. SUBOXONE sublingual film should NOT be chewed, swallowed, or moved after placement. Swallowing the film reduces the bioavailability of the drug.

## **VI. Patient Information**

#### **What information about the safe use of SUBOXONE 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 SUBOXONE 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 SUBOXONE, urgent medical attention should be sought immediately

- Advise patients that SUBOXONE contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their SUBOXONE in a safe place and to protect them from theft
- Instruct patients never to give SUBOXONE 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 SUBOXONE is against the law
- Caution patients that SUBOXONE 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 SUBOXONE without consulting their prescriber
- After treatment induction, advise patients to take SUBOXONE once a day as directed
- Inform patients that SUBOXONE 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 SUBOXONE 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, SUBOXONE 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 SUBOXONE during pregnancy
- Advise nursing mothers treated with SUBOXONE 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 SUBOXONE
- 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 flushed down the toilet

## **VII. Where Can I Get More Information on Treating Patients With SUBOXONE Sublingual Film?**

Refer to the package insert for Full Prescribing Information which can be found at [www.SuboxoneFilmREMS.com](http://www.SuboxoneFilmREMS.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](http://www.asam.org))
- American Academy of Addiction Psychiatry website ([www.aaap.org](http://www.aaap.org))
- Physician Clinical Support System - Buprenorphine ([www.pcssmat.org](http://www.pcssmat.org))

SUBOXONE® is a registered trademark of Reckitt Benckiser Healthcare (UK) Ltd.

## 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.

Manufactured for Reckitt Benckiser Pharmaceuticals Inc.  
Richmond, VA 23235 by MonoSol Rx LLC, Warren, NJ 07059

Copyright © 2014 Reckitt Benckiser Pharmaceuticals Inc.  
April 2014  
Printed in USA



## Risk Evaluation and Mitigation Strategy (REMS)

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII).

A REMS is a strategy to manage known or potential serious risks associated with a drug product and is required by the FDA to ensure that the benefits of a drug outweigh its risks.

The purpose of the Suboxone Film REMS program is to inform healthcare professionals and patients about the safe use conditions and serious risks, including accidental overdose, misuse, and abuse, associated with buprenorphine-containing trans mucosal products indicated for the treatment of opioid dependence.

The REMS program includes various materials and processes developed to assist in achieving the following 2 goals:

- Mitigate the risk of accidental overdose, misuse, and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with SUBOXONE Film

As a healthcare provider, you can take an active role in implementing REMS, which will help to:

- Ensure the safe and proper use of SUBOXONE Film
- Monitor patients for misuse, abuse, and diversion
- Address any issues that arise and allow you to adjust treatment protocols as necessary

### Reference

1. Data on file, Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA.

### Indication:

SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII) is indicated for maintenance treatment of opioid dependence as part of a complete treatment plan to include counseling and psychosocial support.

Treatment should be initiated under the direction of physicians qualified under the Drug Addiction Treatment Act.

### Important Safety Information:

SUBOXONE Sublingual Film should not be used by patients hypersensitive to buprenorphine or naloxone, as serious adverse reactions, including anaphylactic shock, have been reported.

SUBOXONE Sublingual Film can be abused in a manner similar to other opioids, legal or illicit. Clinical monitoring appropriate to the patient's level of stability is essential.

Chronic use of buprenorphine can cause physical dependence. A sudden or rapid decrease in dose may result in an opioid withdrawal syndrome that is typically milder than seen with full agonists and may be delayed in onset.

SUBOXONE Sublingual Film can cause serious life-threatening respiratory depression and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other central nervous system (CNS) depressants (ie, sedatives, tranquilizers, or alcohol). It is extremely dangerous to self-administer nonprescribed benzodiazepines or other CNS depressants while taking SUBOXONE Sublingual Film. Dose reduction of CNS depressants, SUBOXONE Sublingual Film, or both when both are being taken should be considered.

Liver function should be monitored before and during treatment.

Death has been reported in nontolerant, nondependent individuals, especially in the presence of CNS depressants.

Children who take SUBOXONE Sublingual Film can have severe, possibly fatal, respiratory depression. Emergency medical care is critical. Keep SUBOXONE Sublingual Film out of the sight and reach of children.

Intravenous misuse or taking SUBOXONE Sublingual Film before the effects of full-agonist opioids (eg, heroin, hydrocodone, methadone, morphine, oxycodone) have subsided is highly likely to cause opioid withdrawal symptoms.

Neonatal withdrawal has been reported.

Use of SUBOXONE Sublingual Film in pregnant women or during breast-feeding should only be considered if the potential benefit justifies the potential risk.

Caution should be exercised when driving vehicles or operating hazardous machinery, especially during dose adjustment.

Adverse events commonly observed with the sublingual administration of SUBOXONE Sublingual Film are oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema.

Cytolytic hepatitis, jaundice, and allergic reactions, including anaphylactic shock, have been reported.

This is not a complete list of potential adverse events associated with SUBOXONE Sublingual Film. Please see full Prescribing Information for a complete list.

To report an adverse event associated with taking SUBOXONE Sublingual Film, please call 1-877-782-6966. You are encouraged to report adverse events of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

Please see [full US Prescribing Information](#) and [Medication Guide](#) for SUBOXONE Sublingual Film.

For more information about SUBOXONE® (buprenorphine and naloxone) sublingual tablets (CIII), please see [full US Prescribing Information](#) and [Medication Guide](#).

## Ensuring Appropriate Use

A core element of the REMS is to ensure the benefits of prescribing buprenorphine-containing medications to a patient for treatment of opioid dependence outweigh the risks of accidental overdose, misuse, and abuse. In order to meet the requirements of the REMS, you should take the following measures and document the actions you take to ensure safe use conditions.

- Verify patient meets diagnostic criteria for opioid dependence
- Discuss risks described in SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII) professional labeling and Medication Guide with patient
- Explain or review conditions of safe storage of medication
- Provide induction doses under appropriate supervision
- Prescribe limited amount of medication at first visit
- Assess and encourage patient to take medication as prescribed
  - Consider film count/dose reconciliation
- Assess appropriateness of dosage
  - SUBOXONE Film 16 mg/4 mg is recommended for maintenance
  - Doses higher than this should be an exception
  - The need for higher dose should be carefully evaluated
- Conduct urine drug screens as appropriate to assess use of illicit substances
- Assess participation in professional counseling and support services
- Assess whether benefits of treatment with buprenorphine-containing products outweigh risks associated with SUBOXONE Film
- Assess whether patient is making adequate progress toward treatment goals
  - Consider results of urine drug screens as part of the evidence of the patient complying with the treatment program
  - Consider referral to more intensive forms of treatment for patients not making progress
- Schedule next visit at interval commensurate with patient stability
  - Weekly, or more frequent visits, are recommended for the first month

As part of the SUBOXONE REMS, prescribers of SUBOXONE Sublingual Film 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 (eg, 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 or by calling 1-877-782-6966.

## Educating Patients About Treatment

The [SUBOXONE® \(buprenorphine and naloxone\) Sublingual Film \(CIII\) Medication Guide](#) is a core component of the SUBOXONE Film REMS. It contains important information about the product, including proper administration, potential adverse events, and other precautions. You should review the medication guide with patients for whom you prescribe SUBOXONE Film to ensure that they understand the proper use and safety precautions associated with SUBOXONE Film. You have received a tear pad with medication guides that you can distribute to patients. If you require additional copies of the medication guide, you can request them through your Clinical Liaison or by calling 1-877-782-6966. The [SUBOXONE Film Medication Guide](#) is also available to download at [suboxone.com](#).

Additionally, tear pads of the medication guides are provided to pharmacies that order and dispense SUBOXONE Film with reminders that they should provide the [SUBOXONE Film Medication Guide](#) with every SUBOXONE Film prescription.

**Messages that need to be communicated to patients about the risks of accidental overdose, misuse, and abuse include the following:**

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other central nervous system (CNS) depressants (including alcohol) while taking SUBOXONE or SUBUTEX® (buprenorphine) CIII. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician
- Patients should be advised that SUBOXONE and SUBUTEX contain an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their Film or tablets in a safe place, and to protect them from theft
- Patients should be instructed to keep SUBOXONE and SUBUTEX in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE or SUBUTEX, medical attention should be sought immediately
- Patients should be advised never to give SUBOXONE or SUBUTEX to anyone else, even if he or she has the same signs and symptoms. It may harm them and it is against the law
- Patients should be instructed to dispose of unused doses of SUBOXONE or SUBUTEX by flushing the tablets or films down the toilet

Additional information about safe use conditions and patient monitoring can be found in the [Prescriber Brochure](#) and in the warning and precautions sections of the full [Prescribing Information](#).

Further information is available by calling the Reckitt Benckiser Pharmaceuticals Inc. Medical Information Unit at 1-877-SUBOXONE (782-6966) or on [suboxone.com](#).

### Reference

1. Data on file, Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA.



## Resources For Healthcare Professionals

The materials used to ensure the safe use of SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII), in addition to the prescribing information and the medication guide, include

- [REMS Instruction Letter to Prescribers](#)
- [REMS Instruction Letter to Pharmacists](#)
- [Appropriate Use Checklist](#)
- [Prescriber Brochure](#)
- [Pharmacist Brochure](#)
- [Medication Guide](#)
- [SUBUTEX® \(buprenorphine\) \(CIII\) Prescribing Information](#)
- [SUBUTEX Medication Guide](#)
- [SUBOXONE® \(buprenorphine and naloxone\) Sublingual Tablet \(CIII\) Prescribing Information](#)
- [SUBOXONE Tablet Medication Guide](#)

The content of these materials is consistent with the Prescribing Information (PI) for the product and includes information on the REMS program and the elements to assure safe use. They convey the most critical information necessary to ensure the safe use of the product.

Copies of these materials are also available by request through a toll-free information number (1-877-782-6966), and through Clinical Liaisons.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

BOB A RAPPAPORT  
04/28/2014