NDA 20-732
SUBUTEX® (buprenorphine) sublingual tablet CIII

Buprenorphine (opioid partial agonist-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 SUBUTEX tablets dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

I. GOAL(S):

The goals of the SUBUTEX tablet risk evaluation and mitigation strategy are to:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform patients of the serious risks associated with SUBUTEX tablet

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each SUBUTEX tablet prescription in accordance with 21 CFR 208.24.

B. Elements to Assure Safe Use

1. Safe use conditions

a. SUBUTEX tablets 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 SUBUTEX Tablet REMS, a REMS Instruction Letter to Prescribers 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 SUBUTEX, as well as the need to appropriately monitor patients and document safe use conditions. Annual mailings will occur in September of each year 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 following materials will be appended to the Prescriber Instruction Letter: Medication Guide, Full Prescribing Information, Physician Brochure, 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 SUBUTEX Tablet REMS, a REMS Introductory Letter for Pharmacists will be mailed to all retail pharmacies authorized by DEA to handle schedule 3 controlled substances on a national mailing list from the National Technical Information Service. The following materials will be appended to the Introductory Pharmacist Letter:

Medication Guide, Full Prescribing Information and the Pharmacist Brochure.

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 product website.

2. Monitoring

a. Each patient using SUBUTEX tablets 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:

- SUBUTEX tablet Medication Guide
- REMS Instruction Letter to Prescribers
- REMS Introductory Letter to Pharmacists
- Appropriate Use Checklist

- Physician Brochure, *"Important Information for Physicians-Frequently Asked Questions"*
- Pharmacist Brochure, *"Important Information for Pharmacists-Frequently Asked Questions"*

C. Implementation System

The Implementation System includes the following:

1. Reckitt Benckiser Pharmaceuticals Inc. will ensure that all DATA 2000-certified physicians receive the Instruction 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 the first REMS assessments to FDA by August 31, 2012, the second REMS assessment by February 28, 2013, the third REMS assessment by August 31, 2013, and 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
SUBUTEX® (Sub-u-tex)
(buprenorphine)
Sublingual Tablet (CIII)

IMPORTANT:

Keep SUBUTEX 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 SUBUTEX, get emergency help right away.

Read this Medication Guide before you start taking SUBUTEX 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 SUBUTEX.

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

What is the most important information I should know about SUBUTEX sublingual tablets?

- SUBUTEX 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 you

  These can be signs of an overdose or other serious problems.
- SUBUTEX contains an opioid that can cause physical dependence.
  - Do not stop taking SUBUTEX 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
  - SUBUTEX is not for occasional or “as needed” use
- An overdose, and even death, can happen if you take benzodiazepines, sedatives, tranquilizers, or alcohol while using SUBUTEX. 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”) SUBUTEX.

  - Injecting this medicine may cause life-threatening infections and other serious health problems.
  - Injecting SUBUTEX may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems and cravings.
- In an emergency, have family members tell the emergency department staff that you are physically dependent on an opioid and are being treated with SUBUTEX.

What is SUBUTEX sublingual tablet?

- SUBUTEX is a prescription medicine used to begin treatment in adults who are addicted to (dependent on) opioid drugs (either prescription or illegal drugs), as part of a complete treatment program that also includes counseling and behavioral therapy.
- SUBUTEX is most often used for the first 1 or 2 days to help you start with treatment.

SUBUTEX 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 SUBUTEX in a safe place to protect it from theft. Never give your SUBUTEX to anyone else; it can cause death or harm them. Selling or giving away this medicine is against the law.

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

Who should not take SUBUTEX sublingual tablets?

Do not take SUBUTEX if you are allergic to buprenorphine.

What should I tell my doctor before taking SUBUTEX sublingual tablets?

SUBUTEX may not be right for you. Before taking SUBUTEX, 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 SUBUTEX will harm your unborn baby. If you take SUBUTEX 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. SUBUTEX can pass into your milk and may harm the baby. Talk to your doctor about the best way to feed your baby if you take SUBUTEX. Breast feeding is not recommended while taking SUBUTEX.

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

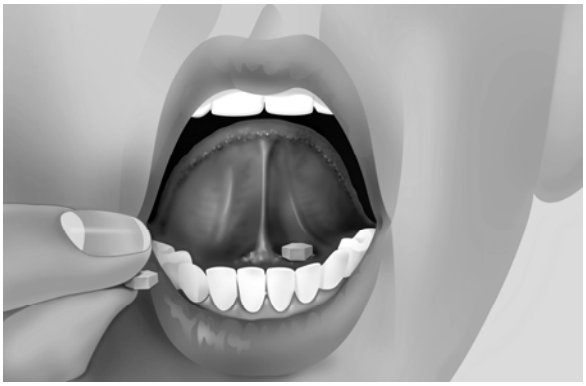
Sometimes the doses of certain medicines and SUBUTEX may need to be changed if used together. Do not take any medicine while using SUBUTEX until you have talked with your doctor. Your doctor will tell you if it is safe to take other medicines while you are using SUBUTEX.

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

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

How should I take SUBUTEX sublingual tablets?

- Always take SUBUTEX 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 SUBUTEX more often than prescribed by your doctor.
- If you are prescribed a dose of 2 or more SUBUTEX tablets at the same time:
  - Ask your doctor for instructions on the right way to take SUBUTEX tablets
  - Follow the same instructions every time you take a dose of SUBUTEX tablet
- Put the tablets under your tongue. Let them dissolve completely.



- While SUBUTEX is dissolving, do not chew or swallow the tablet because the medicine will not work as well.
- Talking while the tablet is dissolving can affect how well the medicine in SUBUTEX is

absorbed.

- If you miss a dose of SUBUTEX, 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 SUBUTEX 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 SUBUTEX the right way.
- **If you take too much SUBUTEX or overdose, call Poison Control or get emergency medical help right away.**

What should I avoid while taking SUBUTEX sublingual tablets?

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

What are the possible side effects of SUBUTEX sublingual tablets?

SUBUTEX can cause serious side effects including:

- **See "What is the most important information I should know about SUBUTEX sublingual tablets?"**
- **Respiratory problems.** You have a higher risk of death and coma if you take SUBUTEX 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 SUBUTEX.
- **Allergic reaction.** You may have a rash, hives, swelling of your face, wheezing, or 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 SUBUTEX sublingual tablets include:

- Headache
- Nausea
- Vomiting
- Increased sweating
- Constipation
- Drug withdrawal syndrome
- Decrease in sleep (insomnia)
- Pain

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 SUBUTEX sublingual tablet. 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 SUBUTEX sublingual tablets?

- Store SUBUTEX between 59°F and 86°R (15°C to 30°C).
- **Keep SUBUTEX in a safe place, out of the site and reach of children.**

How should I dispose of unused SUBUTEX sublingual tablets?

- Dispose of unused SUBUTEX sublingual tablets as soon as you no longer need them.
- Flush unused tablets down the toilet.

General information about the safe and effective use of SUBUTEX sublingual tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SUBUTEX for a condition for which it was not prescribed. Do not give SUBUTEX 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 SUBUTEX sublingual tablet. 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 SUBUTEX sublingual tablets?

Active Ingredient: buprenorphine
Inactive Ingredients: lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, and magnesium stearate

Issued December 2011

Manufactured by: Reckitt Benckiser Healthcare (UK) Ltd., Hull, HU8 7DS. UK Dist. by: Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235

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

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

Copyright © 2010 Reckitt Benckiser Pharmaceuticals Inc.
Printed in USA

1-1278-009-US-1211

SUBOXONE® (buprenorphine and naloxone) (CIII)
SUBUTEX® (buprenorphine) (CIII)

IMPORTANT SAFETY INFORMATION FOR PRESCRIBERS

<DATE>

Dr. <FIRST NAME> <LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY>, <STATE> <ZIP>

Dear Dr. <LAST NAME>:

Since you are a prescriber certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000), Reckitt Benckiser Pharmaceuticals Inc. is informing you about its new Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE and SUBUTEX. Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of these products in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

The REMS is a requirement from the Food and Drug Administration (FDA) to ensure the benefits of SUBOXONE and SUBUTEX outweigh the risks of accidental overdose, misuse, and abuse. SUBOXONE and SUBUTEX sublingual tablets are indicated for the treatment of opioid dependence. SUBOXONE sublingual film is indicated for the maintenance treatment of opioid dependence. These products should be used as part of a complete treatment plan to include counseling and psychosocial support.

This REMS does not apply to SUBOXONE or SUBUTEX dispensed to patients admitted to Opioid Treatment Programs (OTP) under 42 CFR Part 8 because the care of these patients is subject to specific requirements under those regulations.

Certified prescribers, treating patients outside of OTPs, must meet the requirements of the SUBOXONE and SUBUTEX REMS and ensure safe use conditions. Reckitt Benckiser Pharmaceuticals asks that you take the following ten actions and document the completion of these actions:

- Verify patient meets diagnostic criteria for opioid dependence
- Review Medication Guide with patient
- Provide induction doses under appropriate supervision
- Prescribe a limited amount of medication during the initial stages of treatment

- Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month)
- Consider pill 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

An **Appropriate Use Checklist** is enclosed to assist you in complying with this requirement of the REMS. You may use other means (e.g. electronic health record) specific to your office practice to document that the above actions have been completed for your patient.

In addition, the REMS includes a Medication Guide with important information to be reviewed with patients. Five key messages that need to be communicated to patients about the risks of accidental overdose, misuse, and abuse include:

- Warn patients 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. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician.

- Advise patients 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 tablets in a safe place, and to protect them from theft.

- Instruct patients 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.

- Advise patients never to give SUBOXONE or SUBUTEX 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 this medication is against the law.

Additional important safety information can be in found in the enclosed Prescriber Brochure and the full Prescribing Information.

You are also encouraged to report adverse events from prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

If you have an adverse event to report or any questions, please call our Medical Information Unit at 1-877-SUBOXONE (1-877-782-6966) or go online to www.suboxone.com.

Sincerely,

<NAME>
<TITLE>
Version 3 Revised October 2010

Reckitt Benckiser Pharmaceuticals Inc

Enclosures:

Appropriate Use Checklist
Important Information for Physicians Brochure
Medication Guide
Full Prescribing Information

SUBOXONE® (buprenorphine and naloxone) (CIII)
SUBUTEX® (buprenorphine) (CIII)

IMPORTANT SAFETY INFORMATION FOR PHARMACISTS

<DATE>

<FIRST NAME> <LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY>, <STATE> <ZIP>

Dear <LAST NAME>:

Reckitt Benckiser Pharmaceuticals Inc (RBP) is informing you about its new Risk Evaluation and Mitigation Strategy (REMS) for SUBOXONE and SUBUTEX. Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of these products in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

The REMS is a requirement from the Food and Drug Administration (FDA) to ensure the benefits of SUBOXONE and SUBUTEX outweigh the risks of accidental overdose, misuse, and abuse. SUBOXONE and SUBUTEX sublingual tablets are indicated for the treatment of opioid dependence. SUBOXONE sublingual film is indicated for the maintenance treatment of opioid dependence. These medications should be used as part of a complete treatment plan to include counseling and psychosocial support.

This REMS does not apply to SUBOXONE or SUBUTEX dispensed to patients admitted to Opioid Treatment Programs (OTP) under 42 CFR Part 8 because the care of these patients is subject to specific requirements under those regulations.

The goals of the SUBOXONE and SUBUTEX REMS are to:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform patients of the serious risks associated with SUBOXONE and SUBUTEX

To comply with RBP REMS commitments, we ask that you provide a Medication Guide to your patients or their caregivers with each dispensing and encourage them to read it. The Medication Guide provides important information on the safe and effective use of SUBOXONE and SUBUTEX, and the importance of participating in psychosocial support. Five key messages that should be communicated are:

- Warn patients 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. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician

- Advise patients 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 films or tablets in a safe place, and to protect them from theft

- Instruct patients 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

- Advise patients never to give SUBOXONE or SUBUTEX 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 this medication is against the law

Medication Guides will be provided for SUBOXONE film within the primary packaging of the drug, only for the film formulation. Tear pads of Medication Guides will be provided to pharmacies by RBP for SUBOXONE film and SUBOXONE and SUBUTEX tablets. If you require additional Medication Guides, you may:

- Contact RBP's Medical Information Unit at 1-877-SUBOXONE (1-877-782-6966)

- Print copies from the SUBOXONE website (www.suboxone.com)

Additional important safety information can be found in the enclosed Pharmacist Brochure and the full Prescribing Information.

You are also encouraged to report adverse events from prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

If you have an adverse event to report or any questions, please call our Medical Information Unit at 1-877-SUBOXONE (1-877-782-6966) or go online to *www.suboxone.com*.

Sincerely,

<NAME>

<TITLE>
Version 3 Revised October 2010

Reckitt Benckiser Pharmaceuticals Inc

Enclosures: Medication Guide
Important Information for Pharmacists Brochure
Full Prescribing Information

Reckitt Benckiser Pharmaceuticals Inc.

SUBOXONE® and SUBUTEX® APPROPRIATE USE CHECKLIST

Patient Name: _____

As a healthcare provider who prescribes SUBOXONE® (buprenorphine and naloxone) sublingual film CIII, SUBOXONE® (buprenorphine and naloxone) sublingual tablets CIII, or SUBUTEX® (buprenorphine) sublingual tablets CIII, you may find this checklist a useful reminder of the safe use conditions and monitoring requirements to be addressed during each patient's appointment. These include: 1) understanding and reinforcement of safe use conditions, 2) the importance of psychosocial counseling, and 3) 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 more intensive behavioral treatment environment.

Additional resource: Physician Clinical Support System: http://pcssb.org/

Measurement to Ensure Appropriate Use	**Intake/ Induction**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Date:								
Induction								
Verified patient meets diagnostic criteria for opioid dependence								
Discussed risks described in professional labeling and Medication Guide with patient								
Explained or reviewed conditions of safe storage of medication								
Provided induction doses under appropriate supervision								
Prescribed limited amount of medication at first visit								
Scheduled next visit at interval commensurate with patient stability • Weekly, or more frequent visits recommended for the first month								
Maintenance								
Assessed and encouraged patient to take medication as prescribed • Consider pill count/dose reconciliation								

Reckitt Benckiser Pharmaceuticals Inc.

SUBOXONE® and SUBUTEX® APPROPRIATE USE CHECKLIST

Measurement to Ensure Appropriate Use	Intake/ Induction	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Date:								
Maintenance (continued)								
Assessed appropriateness of dosage • Suboxone 12 mg to16 mg is recommended for maintenance • Doses higher than this should be an exception • The need for higher dose should be carefully evaluated								
Assessed whether patient is receiving the psychosocial support considered necessary								
Assessed whether benefits of treatment with Suboxone outweigh risks associated with Suboxone								
Assessed whether patient is making adequate progress toward treatment goals • Conduct urine drug screens as appropriate to assess use of illicit substances • Consider referral to more intensive forms of treatment for patients not making progress								
Scheduled next visit at interval commensurate with patient stability • Weekly, or more frequent visits are recommended for the first month								

SUBOXONE (buprenorphine and naloxone) sublingual tablets and sublingual film CIII
SUBUTEX (buprenorphine) sublingual tablets CIII
SUBOXONE® and SUBUTEX® are registered trademarks of Reckitt Benckiser Healthcare (UK) Ltd.

Initiating Office-Based Opioid Therapy

Important Information for Physicians

Frequently Asked Questions

SUBUTEX®
(buprenorphine) sublingual tablet CIII

I. Introduction

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) to prescribers of SUBUTEX® (buprenorphine) sublingual tablet CIII who are certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000; See Appendix A)

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

This REMS does not apply to SUBUTEX tablet dispensed to patients admitted to Opioid Treatment Programs under 42 CFR Part 8 because the care of these patients is subject to specific requirements under those regulations.

What is SUBUTEX?

SUBUTEX sublingual tablet is indicated for the treatment of opioid dependence and is preferred for induction. SUBUTEX should be used as part of a complete treatment plan to include counseling and psychosocial support.

SUBUTEX contains the active ingredient buprenorphine HCl. The sublingual tablet formulation is administered sublingually as a single daily dose. SUBUTEX is intended to be part of a treatment plan that includes counseling and/or behavioral therapy.

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 SUBUTEX?

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with SUBUTEX outweigh the potential risks, particularly risks of accidental overdose, misuse, and abuse.

What are the goals of the SUBUTEX REMS?

The goals of the REMS for SUBUTEX are to:

1. Mitigate the risks of accidental overdose, misuse, and abuse
2. Inform physicians, pharmacists, and patients of the serious risks associated with the use of SUBUTEX

What is my role with regard to the REMS for SUBUTEX?

To meet the requirements of the REMS and to ensure the benefits of prescribing SUBUTEX to a patient outweigh the risks of accidental overdose, misuse, and abuse,

physicians 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 SUBUTEX, including those described in the Medication Guide
- Provide induction doses under appropriate supervision
- Prescribe a limited amount of medication during the initial stages of treatment
- Explain how to safely store the medication
- Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended for the first month)
- Consider pill count/dose reconciliation
- Assess whether patient is receiving counseling/psychosocial support considered necessary for treatment
- Assess whether patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing)
- Continually assess appropriateness of maintenance dose
- Continually assess whether or not benefits of treatment outweigh the risks

As part of the REMS, physicians prescribing SUBUTEX for opioid dependence will be provided with an 'Appropriate Use Checklist' to document safe use conditions and clinical monitoring of each patient. This can be retained in the records of each patient.

This REMS does not apply to SUBUTEX tablet dispensed to patients admitted to Opioid Treatment Programs under 42 CFR Part 8 because the care of these patients is subject to specific requirements under those regulations.

III. Highlighted Important Safety Information for SUBUTEX

This section of the brochure highlights important safety information to consider when prescribing SUBUTEX. **Refer to the prescribing information (PI) for detailed safety-related information for SUBUTEX.**

Abuse Potential for SUBUTEX

Is SUBUTEX abusable?

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse, misuse, or diversion of this product.

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.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal request of medication prescribed.

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

SUBUTEX does not contain a naloxone component. Therefore, to discourage misuse or abuse, it is highly recommended that SUBOXONE®* (buprenorphine and naloxone) sublingual film CIII or SUBOXONE (buprenorphine and naloxone) sublingual tablet CIII is prescribed whenever feasible. Because it contains naloxone, SUBOXONE is 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.

Clinicians should also be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route.

Because of the partial agonist properties of buprenorphine, SUBUTEX may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

*SUBOXONE full Prescribing Information can be found at **www.suboxone.com**

Can SUBUTEX cause dependence?

Buprenorphine, the active ingredient in SUBUTEX, 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 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 SUBUTEX to supervised use only during induction, wherever possible. It is strongly recommended that SUBOXONE be used whenever unsupervised administration is planned. Point out to

the patient that SUBOXONE products contain naloxone. The naloxone in SUBOXONE is likely to precipitate withdrawal signs and symptoms when injected by individuals dependent on heroin, morphine, or other full opiate agonists.

- As your patients progress beyond induction to a stabilized dose, consider a longer-term prescription of SUBOXONE to be taken at home. 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
- 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 physician's office within a reasonable period (e.g., 24 to 36 hours) with all prescribed medications. In this case, the number of tablets remaining must correspond to the number expected based on prescribed dosing. If this program is implemented, physicians 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 should be provided or referred for more intensive and structured treatment.

What is an appropriate medical response to overdose on SUBUTEX?

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

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, SUBUTEX sublingual tablet, or both in situations of concomitant prescription
- Store SUBUTEX sublingual tablet 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 SUBUTEX sublingual tablet to patients with known hypersensitivity to buprenorphine
- SUBUTEX sublingual tablet may precipitate opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists if administered sublingually or parenterally before the agonist effects of other opioids have subsided
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- SUBUTEX sublingual tablet is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose
- Caution patients about the risk of driving or operating hazardous machinery

Adverse Reactions

- Adverse events most commonly observed with the sublingual administration of the SUBUTEX sublingual tablet during clinical trials and post-marketing experience are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain
- To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 1-877-SUBOXONE (1-877-782-6966), FDA at 1-800-FDA-1088, or www.fda.gov/medwatch

Drug Interactions

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing

- Use caution in prescribing SUBUTEX sublingual tablet for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse

Use in Specific Populations

- SUBUTEX sublingual tablet is not indicated for use during pregnancy unless potential benefit justifies potential risk
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking SUBUTEX sublingual tablet
- Safety and effectiveness of SUBUTEX sublingual tablet in patients below the age of 16 has not been established
- Administer SUBUTEX sublingual tablet with caution to elderly or debilitated patients
- Administer SUBUTEX sublingual tablet with caution in patients with liver dysfunction

Prescribing SUBUTEX

When should SUBUTEX be prescribed?

SUBUTEX contains no naloxone and is preferred for use only during the induction phase of treatment of opioid dependence. The use of SUBUTEX for unsupervised administration should be limited to those patients who cannot tolerate SUBOXONE; for example, those patients who have been shown to be hypersensitive to naloxone.

What is the proper protocol for induction?

SUBUTEX tablets are preferred for use during induction. Prior to induction, consideration should be given to the type of opioid dependence, the time since last opioid use, and the degree or level of opioid dependence.

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

In patients taking heroin or other short-acting opioids, the dose of SUBUTEX should be administered at least 4 hours after the patient last used opioids or preferably when moderate objective signs of opioid withdrawal appear.

In patients taking methadone or other long-acting opioids, SUBUTEX should be initiated preferably when moderate objective signs of opioid withdrawal appear. Withdrawal signs and symptoms are possible during induction onto buprenorphine. Withdrawal appears more likely in patients maintained on doses greater than 30mg of methadone and when the first buprenorphine dose is administered shortly after the last methadone dose.

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

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 SUBUTEX for take-home use be provided on each of the 2 to 3 daily 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. SUBUTEX 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.

Following induction, SUBOXONE is preferred when clinical use includes unsupervised administration. Once a stable dosage buprenorphine 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 buprenorphine who are making progress toward the treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician'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 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 physician 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 physicians who do not wish to maintain a supply of SUBUTEX 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 with this booklet (see page 21).

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 a physician 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.

Further information is available by calling the toll-free SUBOXONE Help Line at 1-877-SUBOXONE (1-877-782-6966) or by logging onto **www.suboxone.com**.

Will prescriptions be valid at any pharmacy, or will I need to refer patients to a specific location?

Prescriptions specifying SUBUTEX will be valid at any pharmacy. However, prior to prescribing SUBUTEX 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. To reduce patient waiting time, it is recommended that you avail yourself of any call-in or fax-in prescription services offered. Please call the toll-free SUBOXONE Help Line at 1-877-SUBOXONE (1-877-782-6966) or visit **www.suboxone.com** for more information or assistance.

Are there special confidentiality issues I should consider?

Remember that you may be communicating with the pharmacist to verify prescriptions for a particular patient. As you may know, 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 SUBUTEX 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 21). 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 physician, 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 physician to the pharmacist.

To learn more about these regulations, visit the SAMHSA website, *www.hipaa.samhsa.gov*, or call 1-866-BUP-CSAT (1-866-287-2728).

Dosing and Administration of SUBUTEX

How do I maintain clinically effective dosing for stabilized patients?

SUBUTEX contains no naloxone and is preferred for use only during induction. The use of SUBUTEX for unsupervised administration should be limited to those patients who cannot tolerate SUBOXONE or have been shown to be hypersensitive to naloxone.

The recommended target dose of buprenorphine is 16 mg/day. Clinical studies have shown that this is a clinically effective dose. Although doses as low as 12 mg 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 daily dosage of buprenorphine is 24 mg. The reported lack of significant increase in brain mu-receptor occupancy between doses of 16 mg and 32 mg would imply 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 should SUBUTEX be administered?

SUBUTEX is administered sublingually.

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

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

Physicians 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 physician does not feel that he or she has the expertise to manage the patient. In such

cases, the physician may want to assess whether to refer the patient to a specialist and/or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Discontinuing SUBUTEX Therapy

What can I tell patients who wish to discontinue treatment?

Patients should be advised not to change the dose of SUBUTEX without consulting their physician.

Patients seeking to discontinue treatment with SUBUTEX 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 SUBUTEX, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the SUBUTEX dose, rather than abruptly discontinue it. The physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

IV. 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 physicians seeking to obtain the certification to prescribe SUBUTEX must be able to provide or refer patients for counseling.

In addition to services typically provided by physicians, counseling may incorporate such elements as motivational enhancement therapy, cognitive behavioral therapy, prevention education, and intervention in case of relapse.

If counseling is provided by an individual other than the prescribing physician, it is essential that the counselor partner with the physician in providing care. The counselor can provide an additional measure of monitoring for adherence and treatment response.

What safety conditions need to be communicated to patients about SUBUTEX?

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 SUBUTEX. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician

- Advise patients that SUBUTEX contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their tablets in a safe place, and to protect them from theft
- Instruct patients to keep 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 SUBUTEX, medical attention should be sought immediately
- Advise patients never to give SUBUTEX 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 SUBUTEX is against the law
- Caution patients that SUBUTEX 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 SUBUTEX therapy does not adversely affect their ability to engage in such activities
- Advise patients not to change the dose of SUBUTEX without consulting their physician
- Advise patients to take SUBUTEX once a day as directed
- Inform patients that SUBUTEX 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 SUBUTEX for opioid dependence to work closely with their physician on a tapering schedule and apprise them of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment
- Caution patients that, like other opioids, SUBUTEX may produce orthostatic hypotension in ambulatory individuals
- Ask patients if other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used
- Advise patients that women of childbearing potential, who become pregnant, or are planning to become pregnant, should consult their physician regarding the possible effects of using SUBUTEX during pregnancy
- Warn patients that buprenorphine passes into breast milk and breast-feeding is therefore not advised in mothers treated with SUBUTEX
- Ask patients to inform their family members or other appropriate individuals that, in the event of emergency, the treating physician or emergency department staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBUTEX
- Instruct patients to dispose of unused SUBUTEX tablets by flushing the tablets down the toilet

V. Where Can I Get More Information on Treating Patients with SUBUTEX?

Refer to the package insert for full Prescribing Information. 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 website at *www.csat.samhsa.gov*.

Appendix A

Obtaining Eligibility to Prescribe SUBUTEX

The Drug Addiction Treatment Act of 2000 (DATA 2000)

This act enables *qualifying physicians* to receive a *waiver* from the special registration requirements in the Controlled Substances Act for the provision of medication-assisted opioid therapy. This waiver allows qualifying physicians to practice medication-assisted opioid addiction therapy with Schedule III, IV, or V narcotic medications specifically approved by the **Food and Drug Administration (FDA)**. SUBUTEX sublingual tablet is a medication that may be used in medication-assisted therapy under the provisions of DATA 2000.

The **Drug Enforcement Administration (DEA)** assigns the physician a special identification number. DEA regulations require this ID number to be included on all buprenorphine prescriptions for opioid addiction therapy, along with the physician's regular DEA registration number.

Who is qualified to obtain a waiver to prescribe SUBUTEX?

Physicians who:

- Hold a current State Medical License
- Hold a valid DEA registration number
- Meet one or more of the following training requirements:
    - Hold a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
    - Hold an addiction certification from the American Society of Addiction Medicine
    - Hold a subspecialty board certification in addiction medicine from the American Osteopathic Association
    - Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, and the American Psychiatric Association are all authorized to provide this training. Details and website addresses can be found on page 15

AND meet the following criteria:

- Have the capacity to provide or to refer patients for necessary ancillary services, such as psychological therapy

- Agree to limit the number of patients they have in treatment at any one time to the following:
  - 30 patients for the first year
  - 100 patients after the first year

How do I obtain the necessary training to become qualified for the waiver?

The Substance Abuse and Mental Health Services Administration (SAMHSA) also maintains a web page listing of upcoming DATA 2000-qualifying training events and web-based training, which can be found at *http://buprenorphine.samhsa.gov/pls/bwns/training*.

Each of the following organizations has scheduled training sessions. You may contact them directly at the addresses below, or visit their websites.

Additionally, you can call the toll-free SUBOXONE Help Line at 1-877-SUBOXONE (1-877-782-6966) or log on to our website **www.suboxone.com**.

American Academy of Addiction Psychiatry
345 Blackstone Boulevard
1st Floor—Weld
Providence, RI 02906
Telephone: 1-401-524-3076
E-mail: information@aaap.org
Website: www2.aaap.org

American Society of Addiction Medicine
4601 North Park Ave, Upper Arcade #101
Chevy Chase, MD 20815
Telephone: 1-301-656-3920
E-mail: email@asam.org
Website: www.asam.org

American Psychiatric Association
1000 Wilson Boulevard, Suite 1825
Arlington, VA 22209-3901
Telephone: 1-888-357-7924
E-mail: apa@psych.org
Website: www.psych.org

American Osteopathic Association
142 East Ontario Street
Chicago, IL 60611
Telephone: 1-800-621-1773
E-mail: info@osteotech.org
Website: www.osteopathic.org

How do I obtain the waiver?

To receive a waiver to practice opioid addiction therapy with approved Schedule III, IV, or V narcotics, a physician must notify the **Center for Substance Abuse Treatment (CSAT, a component of SAMHSA)** of his or her intent to begin dispensing or prescribing this treatment. This Notification of Intent must be submitted to CSAT before the initial dispensing or prescribing of opioid therapy.

Physicians can complete and submit a Waiver Notification Form (SMA-167) online, via fax, or by traditional mail. It is not mandatory to use the SMA-167 form to submit a waiver notification; however, CSAT does recommend the use of this form, either online or in hard copy, as it contains all the data items necessary to expedite the timely processing of waiver notifications.

The Notification of Intent can be submitted online at *http://buprenorphine.samhsa.gov/howto.html*, or via ground mail or fax.

Substance Abuse and Mental Health Services Administration
Division of Pharmacologic Therapies (DPT)
Attn: Opioid Treatment Waiver Program
One Choke Cherry Road, Room 2-1063
Rockville, MD 20857
Telephone: 1-866-BUP-CSAT (1-866-287-2728)
Fax: 1-240-276-1630

Call CSAT/DPT if you have any questions about the notification process or need help completing the form. They can be reached at 1-240-276-2700.

What happens after my notification is sent to CSAT?

CSAT will communicate with the DEA, review your notification, and then notify the DEA that you are qualified as required by DATA 2000. DATA 2000 allows 45 days for this review process. No later than at the end of that 45-day period, the DEA will issue a unique identification number indicating that you are a qualifying physician under DATA 2000. **DEA regulations require that this number, along with your existing DEA registration number, be included on all prescriptions issued for the treatment of opioid dependence under DATA 2000. You must include these numbers when you write prescriptions for SUBUTEX for the treatment of opioid dependence**. CSAT will send you a letter notifying you of the new DEA identification number that will be assigned. You will subsequently receive a revised DEA registration certificate (showing both numbers).

Do I have to wait 45 days before treating patients?

DATA 2000 envisions physicians notifying CSAT as soon as they are qualified, but makes provisions for those who find themselves in the position of being qualified and needing to treat a patient, but not having notified CSAT. In this case, you must first notify CSAT and the DEA of your intent before treating the patient; this can be done

electronically on the Internet by checking the appropriate box or by faxing in the form included in this booklet to CSAT at 1-240-276-1630.

Once I have been treating patients for a year, how do I arrange to increase my patient limit to 100 patients?

If you meet the following conditions, you may have your patient limit increased to 100 patients.

1. Physicians must currently be authorized under DATA 2000
2. Physicians must have submitted the notification for initial authorization at least 1 year ago
3. Physicians must submit a second notification that conveys the need and intent to treat up to 100 patients and certifies their necessary qualifying criteria and their capacity to refer patients for appropriate counseling and other appropriate ancillary services

You can submit your second notification online at

http://buprenorphine.samhsa.gov/pls/bwns/additional_notification_form?prefilled_or_online=ONLINE

Or print a copy from *http://buprenorphine.samhsa.gov/federal.html* and mail or fax it to SAMHSA.

SAMHSA/CSAT will formally acknowledge your submission of the second notification by letter; however, unless you are notified of the contrary, the "good faith" submission of the second notification permits treatment of up to 100 patients.

How do I get SUBUTEX for use in the office?

State laws vary regarding ordering, storing, and dispensing of controlled substances. If you have a routine supplier of products such as vaccines, or injectable products that you use in your office, that supplier will be able to provide you with SUBUTEX in 2 mg buprenorphine and 8 mg buprenorphine strengths.

What storage and record-keeping requirements are associated with maintenance of a supply of SUBUTEX in my office?

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

In addition, physicians prescribing SUBUTEX 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 physician 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. Physicians must adhere to the special confidentiality requirements of 42 CFR Part 2, which apply to the treatment of patients for drug and alcohol addiction (see page 21).

SUBUTEX® and SUBOXONE® are registered trademarks of Reckitt Benckiser Healthcare (UK) Ltd.

Form SMA-167 – Notification of Intent to Use Schedule III, IV, or V Opioid Drugs for Maintenance and Detoxification Treatment of Opiate Addiction under 21 USC §823(g)(2)

Notification of Intent to Use Schedule III, IV, or V Opioid Drugs for the Maintenance and Detoxification Treatment of Opiate Addiction under 21 USC § 823(g)(2)	Form Approved: 0930-0234 Expiration Date: 05/31/2012 See OMB Statement on Reverse DATE OF SUBMISSION

Note: Notification is required by § 303(g)(2), Controlled Substances Act (21 USC § 823(g)(2)). See instructions on reverse. **For second notifications, you must complete items 6, 8, 9, 10, and sign and date the form (item 12).**

1a. NAME OF PRACTITIONER

b. State Medical License Number **c. DEA Registration Number**

2. ADDRESS OF PRIMARY LOCATION *(Include Zip Code) (See instruction below)*	**3. TELEPHONE NUMBER** *(Include Area Code)* **4. FAX NUMBER** *(Include Area Code)* **5. EMAIL ADDRESS** *(Optional)*

6. PURPOSE OF NOTIFICATION *(See instruction below)*

☐ New Notification ☐ New Notification, with the intent to immediately facilitate treatment of an individual (one) patient
☐ Second Notification of need and intent to treat up to 100 patients

7. CERTIFICATION OF USE OF NARCOTIC DRUGS UNDER THIS NOTIFICATION

☐ **I certify that I will only use Schedule III, IV, or V drugs or combinations of drugs that have been approved by the FDA for use in maintenance or detoxification treatment and that have not been the subject of an adverse determination.**

8. CERTIFICATION OF QUALIFYING CRITERIA

I certify that I meet at least one of the following criteria and am therefore a qualifying physician *(Check and provide copies of documentation for all that apply)*:

☐ Subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
☐ Addiction certification from the American Society of Addiction Medicine
☐ Subspecialty board certification in addiction medicine from the American Osteopathic Association
Completion of not less than eight hours of training for the treatment and management of opioid-dependent patients provided by the following organization(s): Date and location of training
- ☐ American Society of Addiction Medicine _____
- ☐ American Academy of Addiction Psychiatry _____
- ☐ American Medical Association _____
- ☐ American Osteopathic Association _____
- ☐ American Psychiatric Association _____
- ☐ Other *(Specify, include date and location)* _____

☐ Participation as an investigator in one or more clinical trials leading to the approval of a Schedule III, IV, or V narcotic drug for maintenance or detoxification treatment
☐ State medical licensing board-approved experience or training in the treatment and management of opioid-dependent patients
☐ OTHER *(Specify)* _____

☐ **For Second Notifications** - I certified qualifications in my initial notification and these qualifications have not changed.

9. CERTIFICATION OF CAPACITY

☐ **I certify that I have the capacity to refer patients for appropriate counseling and other appropriate ancillary services.**

10. CERTIFICATION OF MAXIMUM PATIENT LOAD

☐ **I certify that I will not exceed 30 patients for maintenance or detoxification treatment at one time.**
☐ **Second Notification - I need to treat up to 100 patients and I certify that I will not exceed 100 patients for maintenance or detoxification treatment at one time.**

11. CONSENT TO RELEASE IDENTIFYING INFORMATION TO SAMHSA BUPRENORPHINE PHYSICIAN AND TREATMENT PROGRAM LOCATOR WEB SITE *(Read instruction 11 below before answering)*

☐ I consent to the release of my name, primary address, and phone number to the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site.

☐ I do not consent to the release of my name, primary address, and phone number to the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site.

12. I certify that the information presented above is true and correct to the best of my knowledge. I certify that I will notify SAMHSA at the address below if any of the information contained on this form changes. Note: Any false, fictitious, or fraudulent statements or information presented above or misrepresentations relative thereto may violate Federal laws and could subject you to prosecution, and/or monetary penalties, and or denial, revocation, or suspension of DEA registration. (See 18 USC § 1001; 31 USC §§ 3801-3812; 21 USC § 824.)

Signature _____ Date _____

Please send the completed form to:
Substance Abuse and Mental Health Services Administration
Division of Pharmacologic Therapies
Attention: Opioid Treatment Waiver Program
One Choke Cherry Road, Rm 2-1063
Rockville, MD 20857
Fax 240-276-1630
Phone 1-866-287-2728 (1-866-BUP-CSAT)

This form is intended to facilitate the implementation of the provisions of 21 USC § 823(g)(2). The Secretary of DHHS will use the information provided to determine whether practitioners meet the qualifications for waivers from the separate registration requirements under the Controlled Substances Act (21 USC § 823(g)(1)). The Drug Enforcement Administration will assign an identification number to qualifying practitioners and the number will be included in the practitioner's registration under 21 USC § 823(f).

This form may be completed and submitted electronically (including facsimile) to facilitate processing.

1. The practitioner must identify the DEA registration number issued under 21 USC § 823(f) to prescribe substances controlled in Schedules III, IV, or V.	2. Only one address should be specified. For the practitioner to dispense the narcotic drugs or combinations to be used under this notification, the primary address listed here must be the same primary address listed in the practitioner's registration under § 823(f).

6. Purpose of notification:

New Notification - an initial notification for a waiver submitted for the purpose of obtaining an identification number from DEA for inclusion in the registration under 21 USC § 823(f).

New Notification, with the intent to immediately facilitate treatment of an individual (one) patient - an initial notification submitted for the purpose described above, with the additional purpose of notifying the Secretary and the Attorney General of the intent to provide immediate opiate addiction treatment for an individual (one) patient pending processing of this waiver notification.

Second Notification - For physicians who submitted a new notification not less than one year ago and intend and need to treat up to 100 patients. (See Office of National Drug Control Policy Reauthorization Act of 2006.)

11. The SAMHSA Buprenorphine Physician and Treatment Program Locator Web site is publicly accessible at http://buprenorphine.samhsa.gov/bwns_locator/. The Locator Web site lists the names and practice contact information of physicians with DATA waivers who agree to be listed on the site. The Locator Web site is used by the treatment-seeking public and health care professionals to find physicians with DATA waivers. The Locator Web site additionally provides links to many other sources of information on substance abuse. No physician listings on the SAMHSA Buprenorphine Physician and Treatment Program Locator Web site will be made without the express consent of the physician.

PRIVACY ACT INFORMATION

Authority: Section 303 of the Controlled Substances Act of 1970 (21 USC § 823(g)(2)).
Purpose: To obtain information required to determine whether a practitioner meets the requirements of 21 USC § 823(g)(2).
Routine Uses: Disclosures of information from this system are made to the following categories of users for the purposes stated:
A. Medical specialty societies to verify practitioner qualifications.
B. Other federal law enforcement and regulatory agencies for law enforcement and regulatory purposes.
C. State and local law enforcement and regulatory agencies for law enforcement and regulatory purposes.
D. Persons registered under the Controlled Substance Act (PL 91-513) for the purpose of verifying the registration of customers and practitioners.

Effect: This form was created to facilitate the submission and review of waivers under 21 USC § 823(g)(2). This does not preclude other forms of notification.

Paperwork Reduction Act Statement

Public reporting burden for completing this form is estimated to average 4 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the completed form. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this project is 0930-0234. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to SAMHSA Reports Clearance Officer; Paperwork Reduction Project (0930-0234); Room 7-1-1044, One Choke Cherry Road, Rockville, MD 20857

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 which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specify date, event, or condition, i.e. termination of treatment)

Notice to accompany disclosure:

Each disclosure made with the patient's written consent must be accompanied by the following written statement:

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

Version 1.1 Revised November 2011
Mfd. by: Reckitt Benckiser Healthcare (UK) Ltd, Hull, HU8 7DS. UK
Dist. by: Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235
Copyright © 2011 Reckitt Benckiser Pharmaceuticals Inc.
Printed in USA

1-1278-013-US-1111

Initiating Office-Based Opioid Therapy

Important Information for Pharmacists

Frequently Asked Questions

SUBUTEX®
(buprenorphine) sublingual tablet CIII

I. Introduction

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

This REMS does not apply to SUBUTEX tablet dispensed to patients admitted to Opioid Treatment Programs under 42 CFR Part 8 because the care of these patients is subject to specific requirements under these regulations.

What is SUBUTEX sublingual tablet?

SUBUTEX sublingual tablet is indicated for the treatment of opioid dependence and is preferred for induction. SUBUTEX should be used as part of a complete treatment plan to include counseling and psychosocial support.

SUBUTEX contains the active ingredient buprenorphine HCl. The sublingual tablet formulation is administered sublingually as a single daily dose. SUBUTEX is intended to be part of a treatment plan that includes counseling and/or behavioral therapy.

When is SUBUTEX prescribed?

SUBUTEX sublingual tablets contain no naloxone and are preferred for use only during induction. Following induction, SUBOXONE®* (buprenorphine and naloxone) sublingual film CIII or SUBOXONE®* (buprenorphine and naloxone) sublingual tablet CIII is preferred, due to the presence of naloxone, during unsupervised administration. Naloxone is included in the SUBOXONE formulation and is intended to deter individuals from abusing it by the intravenous route. Therefore, while you may see prescriptions for small amounts of SUBUTEX presented for induction doses, you should expect the majority of prescriptions to be for SUBOXONE.

SUBUTEX is controlled as a Schedule III narcotic under the Controlled Substances Act.

*SUBOXONE full Prescribing Information can be found at **www.suboxone.com**.

II REMS – Risk Evaluation and Mitigation Strategy

What is a REMS ?

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

Is there a REMS for SUBUTEX?

Yes, a REMS has been implemented as part of the FDA requirements to ensure that the benefits of treatment with SUBUTEX outweigh the potential risks, particularly risks of accidental overdose, misuse, and abuse.

What are the goals of the REMS for SUBUTEX?

The goals of the REMS for SUBUTEX are to:

1. Mitigate the risks of accidental overdose, misuse, and abuse
2. Inform physicians, pharmacists, and patients of the serious risks associated with the use of SUBUTEX

What is my role with regard to the REMS for SUBUTEX?

As part of the REMS, pharmacists dispensing SUBUTEX for opioid dependence must supply a SUBUTEX Medication Guide with each prescription. The SUBUTEX Medication Guide is available by calling 1-877-782-6966, contacting a Reckitt Benckiser representative or downloading copies at **www.suboxone.com**.

What is the role of the pharmacist in ensuring safe use of SUBUTEX?

As a pharmacist, you will play an important role in ensuring that SUBUTEX is used safely and appropriately. Each time you fill a prescription for SUBUTEX, make sure to:

- Verify that the prescription you receive is from a physician who is in compliance with the provisions of DATA 2000
- Keep in mind that a limited supply of SUBUTEX should be dispensed during the initiation of therapy. This is due to the need of physicians 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
- Advise patients that SUBUTEX should be stored in a safe place to protect the medication from theft since it has the potential to be misused, diverted, and abused. Unused doses of SUBUTEX should be flushed down the toilet
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple prescribers

This REMS does not apply to SUBUTEX tablet dispensed to patients admitted to Opioid Treatment Programs under 42 CFR Part 8 because the care of these patients is subject to specific requirements under these regulations.

III. Highlighted Important Safety Information for SUBUTEX

This section of the brochure highlights important safety information to consider when prescribing or dispensing SUBUTEX**. Please refer to the prescribing information for detailed safety-related information for SUBUTEX**.

Abuse Potential of SUBUTEX

Is SUBUTEX abusable?

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

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.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

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

SUBUTEX does not contain a naloxone component. Therefore, to discourage misuse, diversion, or abuse, it is highly recommended that SUBOXONE is prescribed whenever feasible. Because it contains naloxone, SUBOXONE is 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

Pharmacists should also be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route.

Because of the partial agonist properties of buprenorphine, SUBUTEX may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

Can SUBUTEX cause dependence?

Buprenorphine, the active ingredient in SUBUTEX, 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 concern about an increased risk of misuse, diversion, or abuse.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine, alcohol, and other substances, especially benzodiazepines.

Be sure to read the full Prescribing Information for complete Warnings and Precautions.

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 physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

What is an appropriate medical response to an overdose on SUBUTEX?

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.

How can patients prevent accidental exposure to SUBUTEX in children?

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

Contraindications

- Hypersensitivity to buprenorphine

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, SUBUTEX sublingual tablet, or both in situations of concomitant prescription
- Store SUBUTEX sublingual tablet 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 SUBUTEX sublingual tablet to patients with known hypersensitivity to buprenorphine
- SUBUTEX sublingual tablet may precipitate opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists if administered sublingually or parenterally before the agonist effects of other opioids have subsided

- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- SUBUTEX sublingual tablet is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose
- Caution patients about the risk of driving or operating hazardous machinery

Adverse Reactions

What are the commonly observed adverse events of SUBUTEX?

- Adverse events most commonly observed with the sublingual administration of the SUBUTEX sublingual tablet during clinical trials and post-marketing experience are headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, and pain

- To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 1-877-SUBOXONE (1-877-782-6966), FDA at 1-800-FDA-1088, or www.fda.gov/medwatch

Drug Interactions

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

Use in Specific Populations

- SUBUTEX sublingual tablet is not indicated for use during pregnancy unless potential benefit justifies potential risk
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking SUBUTEX sublingual tablet
- Safety and effectiveness of SUBUTEX sublingual tablet in patients below the age of 16 has not been established
- Administer SUBUTEX sublingual tablet with caution to elderly or debilitated patients
- Administer SUBUTEX sublingual tablet with caution in patients with liver dysfunction

This is not a complete list of potential adverse events associated with SUBUTEX sublingual tablet. Please see full Prescribing Information for a complete list.

To report an adverse event caused by taking SUBUTEX sublingual tablet, please call 1-877-782-6966. You are encouraged to report adverse events of prescription drugs to the FDA. Visit *www.fda.gov/medwatch*, or call 1-800-FDA-1088.

IV. Supplying and Administering SUBUTEX

How is SUBUTEX supplied?

SUBUTEX is supplied as uncoated oval white tablets in 2 dosage strengths:

- NDC 12496-1278-2 (2 mg buprenorphine/tablet) is imprinted with a sword logo on one side and "B2" on the reverse side —30 tablets per bottle
- NDC 12496-1310-2 (8 mg buprenorphine/tablet) is embossed with a sword logo on one side and "B8" on the reverse side —30 tablets per bottle

How should SUBUTEX be administered?

SUBUTEX is administered sublingually.

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

V. Patient Information

What information should I relay to patients about the safe use of SUBUTEX?

The safety concerns related to the use of SUBUTEX includes, but are not limited to, the following:

- Warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBUTEX. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician
- Advise patients that SUBUTEX contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their tablets in a safe place and to protect them from theft
- Instruct patients to keep 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 SUBUTEX, medical attention should be sought immediately
- Advise patients never to give SUBUTEX 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 SUBUTEX is against the law

- Caution patients that SUBUTEX may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken, especially during drug induction and dose adjustments and until they are reasonably certain that SUBUTEX does not adversely affect their ability to engage in such activities
- Advise patients not to change the dose of SUBUTEX without consulting their physician
- Advise patients to take SUBUTEX once a day as directed
- Inform patients that SUBUTEX 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 SUBUTEX for opioid dependence to work closely with their physician on a tapering schedule, and apprise of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment
- Caution patients that, like other opioids, SUBUTEX 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 that women of childbearing potential, who become pregnant or are planning to become pregnant, should consult their physician regarding the possible effects secondary to using SUBUTEX during pregnancy
- Warn patients that buprenorphine passes into breast milk and breast-feeding is therefore not advised in mothers treated with SUBUTEX
- Ask patients to inform their family members or other appropriate individuals that, in the event of emergency, the treating physician or emergency department staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBUTEX
- Instruct patients to dispose of unused doses of SUBUTEX tablets by flushing the tablets down the toilet

Appendix A

Important information to consider before filling prescriptions for Schedule CIII controlled substances

Who is qualified to prescribe SUBUTEX?

DATA 2000 limits office-based use of SUBUTEX to physicians who have met qualifications to receive a waiver.

Waivers to prescribe the product are given to physicians who:

- Hold a current State Medical License
- Hold a valid DEA registration number
- Meet one or more of the following training requirements*:*
    - Hold a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
    - Hold an addiction certification from the American Society of Addiction Medicine
    - Hold a subspecialty board certification in addiction medicine from the American Osteopathic Association
    - Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications or other media. The American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association and the American Psychiatric Association are all authorized to provide this training.

In addition, physicians must have the capacity to provide or to refer patients for necessary ancillary services, such as psychosocial therapy.

Physicians must also agree to treat no more than 30 patients at a time during the first year of providing buprenorphine treatment. After a year, they may have the patient limit increased to 100 patients.

How can I be sure a physician is qualified to prescribe SUBUTEX?

Physicians who meet the qualification criteria listed in the previous section must also submit a Notification of Intent form to the Substance Abuse and Mental Health Services Administration (SAMHSA), indicating their intent to use CIII-V opioid drugs for treatment of opioid addiction before doing so. Once all relevant criteria are verified, SAMHSA notifies the DEA that the physician is qualified, and the DEA issues the physician a unique identification number indicating that he or she is a qualifying physician under DATA 2000.

The Center for Substance Abuse Treatment (CSAT) will send a letter informing the physician of the new DEA identification number. The physician will subsequently receive a revised DEA registration certificate (showing both numbers).

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

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

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

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

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

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

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 physician can disclose any information to a third party about a patient's treatment for substance abuse, that physician must first obtain the patient's signed consent.

When a physician directly transmits a SUBUTEX prescription 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, physician'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

To learn more about these regulations, visit the SAMHSA website, *www.hipaa.samhsa.gov*, or call 1-866-BUP-CSAT (1-866-287-2728).

Are there any special storage, record keeping, or other requirements associated with SUBUTEX?

As a Schedule III controlled substance, SUBUTEX 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*. Many states have their own additional requirements for pharmacists dispensing controlled substances. Be sure to check with the appropriate authority in your state. For more information, visit the website of the National Association of Boards of Pharmacy at *www.nabp.net* for links to individual state boards of pharmacy.

What else can I do to help safeguard against diversion?

As a pharmacist, you should understand the pharmacology of buprenorphine especially as it relates to maximum dose. The goal should be to stabilize the patient with a clinically effective dose of buprenorphine. SUBOXONE is preferred for maintenance treatment. Where SUBUTEX is used in maintenance the dosage should be progressively adjusted in increments/decrements of 2 mg or 4 mg to a level that maintains the patient in treatment and suppresses opioid withdrawal effects.

The recommended target dose of buprenorphine is 16 mg/day. Clinical studies have shown that this is a clinically effective dose. Although doses as low as 12 mg 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 daily dosage of buprenorphine is 24 mg. The reported lack of significant increase in brain mu-receptor occupancy between doses of 16 mg and 32 mg would imply 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): Is there any possibility that drug interactions are affecting buprenorphine metabolism? What are the specific complaints about the dosage? Are the buprenorphine effects wearing off throughout the day? If so, use clinical judgment to guide dosing intervals. 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.

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

However, even if you determine that an individual prescription is legitimate, you should still be aware of other means by which patients may attempt to divert their prescriptions. For example, an opioid user may present themselves to 2 or more qualified prescribers and therefore, receive multiple prescriptions for SUBUTEX. If a patient brings you more than 1 prescription covering the same therapeutic period, you have a legal duty to recognize that they may not be for therapeutic use. You should contact each prescriber for verification and notify them of the additional pending prescription.

In addition, you should be aware that federal rules allow physicians who submitted their first notification of intent more than 1 year ago to treat up to 100 patients with buprenorphine at any one time upon re-notification. Physicians who submitted their first notification of intent less than 1 year ago are limited to 30 patients. Obviously, as patients enter and leave treatment, each physician can treat to his or her specific patient limit over the course of time. However, if you notice an extraordinary number of new prescriptions from a single physician, you may wish to check with the prescriber to determine whether the prescriptions might be fraudulent. Or, if you believe the prescriptions are the result of inappropriate medical practice, contact your state pharmacy or medical board(s).

For more information, call our toll-free help line at 1-877-SUBOXONE (1-877-782-6966) or visit our website at **www.suboxone.com.**

How can I help ensure the success of treatment with SUBUTEX?

As a pharmacist, you are in a unique position to help local physicians implement office-based treatment of opioid dependence with SUBUTEX. One of the most important functions you provide is counseling patients.

Patient Counseling Checklist

- ✓ Communicate and reinforce the importance of counseling, in combination with pharmacotherapy with SUBUTEX, for improving the likelihood of successful treatment
- ✓ Understand the importance of maintaining patient confidentiality
    - People who are opioid-dependent are more likely to seek and continue with treatment when they know their treatment will be held in strict confidence
- ✓ Enhance patient confidentiality by providing a private area for patient counseling
- ✓ Counsel patients on the proper way to take SUBUTEX
- ✓ Take into consideration that:
    - These patients may be experiencing uncomfortable symptoms
    - An accepting, positive attitude is critically important to these patients
- ✓ Remind patients about the importance of proper storage to minimize risk of unintentional pediatric exposure, misuse, diversion, and abuse

Where can I get more information on treating opioid addiction with SUBUTEX?

- Refer to the package insert for full information on the adverse reactions seen during the clinical trials using buprenorphine for opioid dependence treatment
- General information about buprenorphine treatment, and the treatment of addiction are available through numerous sources, such as the SAMHSA website at *www.dpt.samhsa.gov*, the American Society of Addiction Medicine website at *www.asam.org*, and the American Academy of Addiction Psychiatry website at *www2.aaap.org*.

SUBUTEX® and SUBOXONE® are registered trademarks of Reckitt Benckiser Healthcare (UK) Ltd.

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.

Version 1.1 Revised November 2011
Mfd. by: Reckitt Benckiser Healthcare (UK) Ltd, Hull, HU8 7DS. UK
Dist. by: Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235

Copyright © 2011 Reckitt Benckiser Pharmaceuticals Inc.
Printed in USA

1-1278-014-US-1111

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

/s/

JUDITH A RACOOSIN
12/22/2011