

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
22-410/S006/S007

Trade Name: SUBOXONE®

Generic Name: buprenorphine hydrochloride; naloxone hydrochloride

Sponsor: Reckitt Benckiser Pharmaceuticals, Inc.

Approval Date: 8/10/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-410/S006/S007

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-410/S006/S007

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022410/S-006
NDA 022410/S-007

SUPPLEMENT APPROVAL

Reckitt Benckiser Pharmaceuticals, Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Attention: Clorey Toombs
CMC Manager, Regulatory Affairs

Dear Ms. Toombs:

Please refer to your Supplemental New Drug Applications (sNDA) dated September 29 and 30, 2011, and received September 30, 2011, and identified as S-006 and S-007, respectively. These sNDAs were submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Suboxone (buprenorphine and naloxone) sublingual film.

We acknowledge receipt of your amendments dated January 26, March 8, and June 4, 2012, to Supplement S006, and January 27 and 31, March 8, and June 4, 2012, to Supplement S007, and to your risk evaluation and mitigation strategy (REMS) assessment dated August 29, 2011.

These "Prior Approval" supplemental new drug applications provide for the following:

- S-006: addition of a 4 mg/1 mg (buprenorphine/naloxone) strength
- S-007: addition of a 12 mg/3 mg (buprenorphine/naloxone) strength

These supplemental new drug applications also provide for proposed modifications to the approved risk evaluation and mitigation strategy (REMS).

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending

“Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 4, 2012, submission containing final printed carton and container labels.

We remind you of the following:

Pouch Labels (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)

At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence

Carton Labeling (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)

At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Suboxone (buprenorphine and naloxone) sublingual film was originally approved on August 30, 2010. The REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consists of revised REMS and REMS materials to include the following two new dosage strengths as follows:

- 4mg/1mg buprenorphine/naloxone
- 12mg/3mg buprenorphine/naloxone

Your proposed modified REMS, submitted on June 04, 2012, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on August 30, 2010, but (b) (4) has been removed from the REMS document.

There are no changes to the REMS assessment plan described in our August 30, 2010, letter.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022410 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 022410
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022410
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Matthew Sullivan, Senior Regulatory Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Bob A Rappaport, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling

Medication Guide

Carton and Container Labeling

REMS

REMS materials

- REMS Introductory 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”*

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

/s/

BOB A RAPPAPORT
08/10/2012

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

22-410/S006/S007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBOXONE® sublingual film safely and effectively. See full prescribing information for SUBOXONE sublingual film.

SUBOXONE (buprenorphine and naloxone) sublingual film for sublingual administration CIII.

Initial U.S. Approval: 2002

-----INDICATIONS AND USAGE-----

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)

-----DOSAGE AND ADMINISTRATION-----

Administer SUBOXONE sublingual film sublingually as a single daily dose. (2)

The recommended daily dose for maintenance treatment is 16 mg/4mg buprenorphine and naloxone. Advise patients not to cut, chew, or swallow SUBOXONE sublingual film

-----DOSAGE FORMS AND STRENGTHS-----

Sublingual film: 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone. (3)

-----CONTRAINDICATIONS-----

Hypersensitivity to buprenorphine or naloxone. (4)

-----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. (5.1)
- 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). (5.2)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. (5.3)
- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.5)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.6)
- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone. (5.7)

- A marked and intense opioid withdrawal syndrome is highly likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided. (5.8)
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (5.9)
- SUBOXONE sublingual film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose. (5.10)
- Caution patients about the risk of driving or operating hazardous machinery. (5.11)

-----ADVERSE REACTIONS-----

Adverse events commonly observed with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 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. (7.1)
- Use caution in prescribing SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

-----USE IN SPECIFIC POPULATIONS-----

- SUBOXONE sublingual film is not indicated for use during pregnancy unless potential benefit justifies potential risk. (8.1)
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking SUBOXONE sublingual film. (8.3)
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established. (8.4)
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients. (8.5)
- Administer SUBOXONE sublingual film with caution to patients with liver dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised August 2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product 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.

2 DOSAGE AND ADMINISTRATION

SUBOXONE sublingual film is administered sublingually as a single daily dose. SUBOXONE sublingual film should be used in patients who have been initially inducted using SUBUTEX® (buprenorphine) sublingual tablets.

2.1 Maintenance

- SUBOXONE sublingual film is indicated for maintenance treatment. The recommended target dosage of SUBOXONE sublingual film is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose.
- The dosage of SUBOXONE sublingual film should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- The maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage.

2.2 Method of Administration

Do not cut, chew, or swallow SUBOXONE sublingual film. Place a sublingual film under the tongue. If an additional sublingual film is necessary to achieve the prescribed dose, place an additional sublingual film sublingually on the opposite side from the first film. Place the sublingual film in a manner to minimize overlapping as much as possible. The sublingual film must be kept under the tongue until the film is completely dissolved.

SUBOXONE sublingual film should NOT be moved after placement.

Proper administration technique should be demonstrated to the patient.

2.3 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. SUBOXONE sublingual film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the 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 take-home medication.

Ideally 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. Medication 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 progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does 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 medication who are making progress toward their 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 medication toxicity.

2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications 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 re-evaluate the appropriateness of continuing the current treatment.

2.4 Unstable Patients

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/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 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.

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.

2.5 Stopping Treatment

The decision to discontinue therapy with SUBOXONE sublingual film after a period of maintenance should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation of buprenorphine has been used, but the data are insufficient to determine the best method of dose taper at the end of treatment.

2.6 Switching between SUBOXONE Sublingual Tablets and SUBOXONE Sublingual Film

Patients being switched between SUBOXONE sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE sublingual tablets as observed in pharmacokinetic studies [see *Clinical Pharmacology* (12.3)]. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to strips or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

2.7 Switching between SUBOXONE Sublingual Film strengths

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

Table 1. Comparison of available Suboxone film strengths by dimensions and drug concentrations.

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

4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22 mm X 19.2 mm	17.2	4.88

3 DOSAGE FORMS AND STRENGTHS

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in four dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg,
- buprenorphine/naloxone 4 mg/1 mg,
- buprenorphine/naloxone 8 mg/2 mg, and
- buprenorphine/naloxone 12 mg/3 mg

4 CONTRAINDICATIONS

SUBOXONE sublingual film should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported [see *Warnings and Precautions* (5.7)].

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. 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. [see *Drug Abuse and Dependence* (9.2)].

5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBOXONE sublingual film. [see *Drug Interactions* (7.3)].

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

SUBOXONE sublingual film should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

5.3 CNS Depression

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. [see *Drug Interactions* (7.3)].

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children.

5.5 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. 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. [see *Drug Abuse and Dependence* (9.3)]

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual film may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.7 Allergic Reactions

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of SUBOXONE sublingual film.

5.8 Precipitation of Opioid Withdrawal Signs and Symptoms

Because it contains naloxone, SUBOXONE sublingual film 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. Because of the partial agonist properties of buprenorphine, SUBOXONE sublingual film may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

5.9 Neonatal Withdrawal

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus, and there have been reports of convulsions, apnea, respiratory depression, and bradycardia.

5.10 Use in Opioid Naïve Patients

There have been reported deaths of opioid naïve individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBOXONE sublingual film is not appropriate as an analgesic.

5.11 Impairment of Ability to Drive or Operate Machinery

SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that SUBOXONE sublingual film therapy does not adversely affect his or her ability to engage in such activities.

5.12 Orthostatic Hypotension

Like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory patients.

5.13 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.14 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.15 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.16 General Precautions

SUBOXONE sublingual film should be administered with caution in debilitated patients and those with myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Events in Clinical Trials - SUBOXONE sublingual film

The safety of SUBOXONE sublingual film is supported by clinical trials using SUBUTEX (buprenorphine) sublingual tablets and SUBOXONE (buprenorphine and naloxone) sublingual tablets, and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with SUBOXONE sublingual film. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. Few differences in the adverse event profile were noted among SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, SUBUTEX (buprenorphine) sublingual tablets and a buprenorphine ethanolic sublingual solution.

The most common adverse event (>1%) associated with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

Other adverse event data were derived from larger, controlled studies of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) tablets and of buprenorphine sublingual solution. In a comparative study of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) sublingual tablets, adverse event profiles were similar for subjects treated with 16 mg/4 mg SUBOXONE (buprenorphine and naloxone) sublingual tablets or 16 mg SUBUTEX (buprenorphine) sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4-week study of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) sublingual tablets.

Table 2. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine and naloxone) sublingual tablets 16 mg/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) sublingual tablets 16 mg/day N=103 n (%)	Placebo N=107 n (%)
Body as a Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of a buprenorphine ethanolic solution, over a range of doses in four months of treatment. Table 3 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled trial.

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 16-week Study

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose				
	Very Low* N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					

Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:

1 mg solution would be less than a tablet dose of 2 mg

4 mg solution approximates a 6 mg tablet dose

8 mg solution approximates a 12 mg tablet dose

16 mg solution approximates a 24 mg tablet dose

6.2 Adverse Events – Post-marketing Experience with Suboxone Sublingual Tablets

The most frequently reported post-marketing adverse event not observed in clinical trials was peripheral edema.

7 DRUG INTERACTIONS

7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBOXONE sublingual film is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SUBOXONE sublingual film with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered [see Clinical Pharmacology (12.3)].

7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A inducers whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

7.3 Benzodiazepines

There have been a number of post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all, of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and

buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. SUBOXONE sublingual film should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE sublingual film, and should also be cautioned to use benzodiazepines concurrently with SUBOXONE sublingual film only as directed by their physician.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of SUBOXONE sublingual film or buprenorphine/naloxone in pregnant women. SUBOXONE sublingual film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects:

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m² basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Non-teratogenic Effects:

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily

sublingual dose of 16 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

8.3 Nursing Mothers

Buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products.

An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices.

8.4 Pediatric Use

The safety and effectiveness of SUBOXONE sublingual film have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, or SUBUTEX (buprenorphine) sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for signs and symptoms of precipitated opioid withdrawal.

8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product 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.

9.2 Abuse

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 or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for 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 requests 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.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset [see *Warnings and Precautions* (5.5)].

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy [see *Warnings and Precautions* (5.9)].

10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

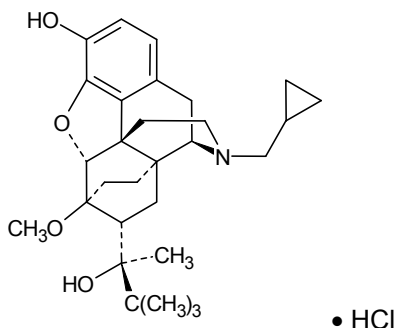
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

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

11 DESCRIPTION

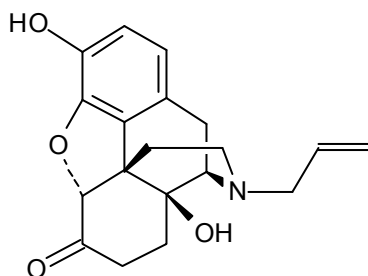
SUBOXONE (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual administration and is available in four dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone. Each sublingual film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5 α -epoxy-3-hydroxy-6-methoxy-6 α ,14-ethano-14 α -morphinan-7 α -yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4 \cdot HCl$ and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



HCl • 2H₂O

Naloxone hydrochloride dihydrate has the molecular formula C₁₉H₂₁NO₄ • HCl • 2H₂O and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBOXONE sublingual film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

12.2 Pharmacodynamics

Subjective Effects:

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8 mg/2 mg and 16 mg/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O₂ saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O₂ saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should 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. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

12.3 Pharmacokinetics**Absorption:**

In pharmacokinetic studies, the 2 mg/0.5 mg and 4 mg/1 mg doses administered as SUBOXONE sublingual films showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets, whereas the 8 mg/2 mg and 12 mg/3 mg doses administered as SUBOXONE sublingual films showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE sublingual tablets. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE sublingual films (total dose of 12 mg/ 3 mg) showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets [See *Dosage and Administration* (2.6 and 2.7)].

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in-vitro; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with SUBOXONE sublingual film, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug-drug Interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual film should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of

CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered [See *Drug Interactions* (7.1)].

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in in-vitro studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity data on SUBOXONE sublingual film are not available.

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Mutagenicity:

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) had no adverse effect on fertility.

16 HOW SUPPLIED / STORAGE AND HANDLING

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine/naloxone 2 mg/0.5 mg/film; content expressed in terms of free base)
- 30 films per carton

- NDC 12496-1204-3 (buprenorphine/naloxone 4 mg/1 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine/naloxone 8 mg/2 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1212-3 (buprenorphine/naloxone 12 mg/3 mg/film; content expressed in terms of free base) - 30 films per carton

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children.

Rx only

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patients should be advised NOT to cut, chew or swallow SUBOXONE sublingual film.

17.1 Safe Use

Before initiating treatment with Suboxone, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time Suboxone is dispensed because new information may be available.

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBOXONE sublingual film. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician. [see *Warnings and Precautions (5.2)*, *Drug Interactions (7.3)*]
- Patients should be advised that SUBOXONE sublingual film contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft.
- Patients should be instructed to keep SUBOXONE sublingual film 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 sublingual film, medical attention should be sought immediately.
- Patients should be advised never to give SUBOXONE sublingual film to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.
- Patients should be cautioned that SUBOXONE sublingual film 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 adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. [see *Warnings and Precautions (5.11)*]
- Patients should be advised not to change the dosage of SUBOXONE sublingual film without consulting their physician.
- Patients should be advised to take SUBOXONE sublingual film once a day.
- Patients should be informed that SUBOXONE sublingual film can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.

- Patients should be cautioned that, like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory individuals. [see *Warnings and Precautions*. (5.12)]
- Patients should inform their physician if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used. [see *Drug Interactions* (7.1, 7.2 and 7.3)]
- Women of childbearing potential who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using SUBOXONE sublingual film during pregnancy. [see *Use in Specific Populations* (8.1)]
- Patients should be warned that buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products. [see *Use in Specific Populations* (8.3)].
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBOXONE sublingual film.
- Refer to the Medication Guide for additional information regarding the counseling information.

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

Distributed by:
Reckitt Benckiser Pharmaceuticals Inc.
Richmond, VA 23235

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

IMPORTANT:

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

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

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

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

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

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

What is SUBOXONE?

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

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

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

Who should not take SUBOXONE?

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

What should I tell my doctor before taking SUBOXONE?

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

- Have trouble breathing or lung problems
- Have an enlarged prostate gland (men)
- Have a head injury or brain problem
- Have problems urinating
- Have a curve in your spine that affects your breathing
- Have liver or kidney problems
- Have gallbladder problems
- Have adrenal gland problems
- Have Addison's disease
- Have low thyroid (hypothyroidism)
- Have a history of alcoholism
- Have mental problems such as hallucinations (seeing or hearing things that are not there)
- Have any other medical condition
- Are pregnant or plan to become pregnant. It is not known if SUBOXONE will harm your unborn baby. If you take SUBOXONE while pregnant, your baby may have symptoms of withdrawal at birth. Talk to your doctor if you are pregnant or plan to

become pregnant.

- Are breast feeding or plan to breast feed. SUBOXONE can pass into your milk and may harm the baby. Talk to your doctor about the best way to feed your baby if you take SUBOXONE. Breast feeding is not recommended while taking SUBOXONE.

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

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

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

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

How should I take SUBOXONE sublingual film?

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



Figure 1

- Before taking SUBOXONE, drink water to moisten your mouth. This helps the film dissolve more easily.

- Hold the film between two fingers by the outside edges.
- **Place SUBOXONE sublingual film under your tongue**, close to the base either to the left or right of the center (see Figure 2).



Figure 2

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

What should I avoid while taking SUBOXONE?

- **Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how this medication affects you.** Buprenorphine can cause

drowsiness and slow reaction times. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative drugs when you take SUBOXONE.

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

What are the possible side effects of SUBOXONE?

SUBOXONE can cause serious side effects, including:

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

Common side effects of SUBOXONE sublingual film include:

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

- Fainting
- Dizziness
- Sleepiness

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

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

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

How should I store SUBOXONE?

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

General information about the safe and effective use of SUBOXONE

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

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

What are the ingredients in SUBOXONE sublingual film?

Active Ingredients: buprenorphine and naloxone.

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

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

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Printed in USA

This Medication Guide has been approved by the US Food and Drug Administration.
Issued: August 2012

526568_4 mg_Carton







**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-410/S006/S007

REMS

Initial REMS Approval: 08/30/2010
Most Recent Modification: 8/2012

SUBOXONE[®] (buprenorphine and naloxone) sublingual film CIII
Buprenorphine (opioid partial agonist-antagonist)

Naloxone (opioid antagonist)

Reckitt Benckiser Pharmaceuticals Inc.

10710 Midlothian Turnpike, Suite 430

Richmond, VA 23235

Telephone: 804-379-1090

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

This REMS does not apply to SUBOXONE film dispensed to patients admitted to an Opioid Treatment Program under 42 CFR Part 8.

I. GOAL(S):

The goals of the SUBOXONE film risk evaluation and mitigation strategy are to:

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

II. REMS ELEMENTS:

A. Medication Guide

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

B. Elements to Assure Safe Use

1. Safe use conditions

- a. SUBOXONE film will only be dispensed by the prescriber or prescribed to patients with documentation of the following safe use conditions:

- i. Verification that the patient meets the diagnostic criteria for opioid dependence.
- ii. Risks described in the professional labeling and the Medication Guide have been discussed with the patient.
- iii. Safe storage of the medication has been explained and reviewed with the patient.
- iv. After appropriate induction, the patient is prescribed a limited amount of medication at the first visit.
- b. Prescribers will document safe use conditions for each patient by using the '[Appropriate Use Checklist](#),' or by using another method (e.g. electronic health record) specific to the prescriber's office practice.
- c. Reckitt Benckiser Pharmaceuticals Inc. will ensure that within 30 days of FDA approval of the SUBOXONE 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 SUBOXONE, as well as the need to appropriately monitor patients and document safe use conditions.
- 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 SUBOXONE REMS, a [REMS Introductory Letter for Pharmacists](#) will be mailed to all pharmacists on a national mailing list from the American Pharmacist Association pharmacies. 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 SUBOXONE film will be subject to the following monitoring:
 - i. Return visits are scheduled at intervals commensurate with patient stability. Weekly, or more frequent, visits are recommended for the first month.
 - ii. Assessment and reinforcement of patient's compliance with the prescribed medication.
 - iii. Assessment of appropriateness of dosage prescribed.
 - iv. Assessment of whether patient is receiving the necessary psychosocial support.
 - v. Assessment of whether patient is making adequate progress towards treatment goals.
- b. Prescribers will document that each patient has received the required clinical monitoring using the 'Appropriate Use Checklist,' or by using another method/system (e.g. electronic health record) specific to the prescriber's office practice.

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

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

III. APPENDICES

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. Six 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 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 (782-6966) or go online to www.suboxone.com.

Sincerely,

<NAME>

<TITLE>

Reckitt Benckiser Pharmaceuticals Inc

Enclosures:

Appropriate Use Checklist

Important Information for Physicians Brochure

Medication Guide

Full Prescribing Information

Rev. 08/2010

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. Six 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 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>

Reckitt Benckiser Pharmaceuticals Inc

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

Rev. 08/2010

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://www.pcssbuprenorphine.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								

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 –16 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

SUBOXONE[®]
(buprenorphine and naloxone) sublingual film CIII

I. Introduction

The purpose of this brochure is to provide information about the Risk Evaluation and Mitigation Strategy (REMS) to prescribers of SUBOXONE® (buprenorphine and naloxone) sublingual film 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 SUBOXONE.

This REMS does not apply to SUBOXONE film 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 SUBOXONE?

SUBOXONE sublingual film is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

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

SUBOXONE includes a second active ingredient, naloxone HCl, at a ratio of 4:1 buprenorphine/naloxone (ratio of free bases). Naloxone is included in the SUBOXONE formulation, and is intended to deter individuals from abusing it by the intravenous route.

How is SUBOXONE sublingual film different from the tablet formulation?

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

Patients being switched between SUBOXONE sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE sublingual tablets as observed in pharmacokinetic studies [*see Clinical Pharmacology (12.3)*]. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to strips or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

As indicated in [Table 1](#), the sizes and the compositions of the four units of SUBOXONE sublingual films, i.e., 2 mg/0.5 mg, 4 mg/2 mg, 8 mg/2 mg and the 12 mg/3 mg units, are

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

Table 1. Comparison of available Suboxone film strengths by dimensions and drug concentrations

Suboxone film unit strength (buprenorphine/naloxone)	Suboxone film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22 mm X 19.2 mm	17.2	4.88

II. REMS – Risk Evaluation and Mitigation Strategy

What is a Risk Evaluation and Mitigation Strategy (REMS)?

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

Is there a REMS for SUBOXONE?

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

What are the goals of the SUBOXONE REMS?

The goals of the REMS for SUBOXONE 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 SUBOXONE

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

To meet the requirements of the REMS and to ensure the benefits of prescribing SUBOXONE 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 SUBOXONE, 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 SUBOXONE 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 SUBOXONE film 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 SUBOXONE

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

Abuse Potential for SUBOXONE

Is SUBOXONE 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.

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

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, SUBOXONE may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

Can SUBOXONE cause dependence?

Buprenorphine, the active ingredient in SUBOXONE is a partial agonist at the mu-opioid receptor. Chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing buprenorphine in situations where there is concern about an increased of misuse, diversion, or abuse.

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

You should consider the following suggestions:

- Initiate treatment with supervised administration, progressing to unsupervised administration as your patient's clinical stability permits

- Limit the use of buprenorphine-only products, such as buprenorphine sublingual tablets to supervised use, wherever possible. Point out to the patient that SUBOXONE 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. It is strongly recommended that SUBOXONE be used whenever unsupervised administration is planned
- 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 pouches 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 SUBOXONE?

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required.

Naloxone hydrochloride may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

Contraindications

Hypersensitivity to buprenorphine or naloxone

Warnings and Precautions

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription
- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events
- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone
- A marked and intense opioid withdrawal syndrome is highly likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- SUBOXONE sublingual film 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 commonly observed with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain and peripheral edema
- 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 SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse

Use in Specific Populations

- SUBOXONE sublingual film 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 SUBOXONE sublingual film
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients
- Administer SUBOXONE sublingual film with caution in patients with liver dysfunction

Prescribing SUBOXONE

When should SUBOXONE be prescribed?

SUBOXONE, which includes naloxone, is indicated for maintenance treatment of opioid dependence and is preferred for unsupervised administration.

What is the proper protocol for induction?

SUBUTEX^{®*} (buprenorphine) sublingual tablets CIII 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 (see package insert for complete instructions).

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 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.

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

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 one to two days of SUBUTEX for take-home use be provided on each of the two to three 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. SUBOXONE should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient assessment.

Once a stable dosage has been achieved and toxicological tests do not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of SUBOXONE who are making progress toward the treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of SUBOXONE toxicity
2. Absence of medical or behavioral adverse effects
3. Responsible handling of SUBOXONE 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 20](#)).

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 SUBOXONE will be valid at any pharmacy. However, prior to prescribing SUBOXONE 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 SUBOXONE prescription, it is recommended that you have the patient sign a release of information at the time of the initial office visit. A sample consent form with all the elements required under 42 CFR Part 2.31 is included with this booklet (see [page 20](#)). 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, <http://www.www.hipaa.samhsa.gov>, or call 1-866-BUP-CSAT (1-866-287-2728).

Dosing and Administration of SUBOXONE

How do I maintain clinically effective dosing for stabilized patients?

The recommended target dose of SUBOXONE 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 SUBOXONE be administered?

SUBOXONE is administered sublingually.

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

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 SUBOXONE Therapy

What can I tell patients who wish to discontinue treatment?

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

Patients seeking to discontinue treatment with SUBOXONE for opioid dependence should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist medication-assisted treatment.

If a dependent patient abruptly discontinues use of SUBOXONE, an opioid abstinence or withdrawal syndrome may develop. If cessation of therapy is indicated, it may be appropriate to taper the SUBOXONE 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 SUBOXONE 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 SUBOXONE?

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 SUBOXONE. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician
- Advise patients that SUBOXONE contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft
- Instruct patients to keep SUBOXONE in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE, medical attention should be sought immediately
- Advise patients never to give SUBOXONE to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death
- Advise patients that selling or giving away SUBOXONE is against the law

- Caution patients that SUBOXONE may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken especially during induction and dose adjustments and until patients are reasonably certain that SUBOXONE therapy does not adversely affect their ability to engage in such activities
- Advise patients not to change the dose of SUBOXONE without consulting their physician
- Advise patients to take SUBOXONE once a day as directed
- Inform patients that SUBOXONE can cause drug dependence of the opioid type. Withdrawal signs and symptoms may occur when the medication is discontinued
- Advise patients seeking to discontinue treatment with SUBOXONE for opioid dependence to work closely with their 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, SUBOXONE 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 SUBOXONE during pregnancy
- Warn patients that buprenorphine passes into breast milk and breast-feeding is therefore not advised in mothers treated with SUBOXONE
- 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 SUBOXONE

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

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 <http://www.csat.samhsa.gov>.

Appendix A

Obtaining Eligibility to Prescribe SUBOXONE

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)**. SUBOXONE sublingual film 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 SUBOXONE?

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:
 - o 30 patients for the first year
 - o 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: www.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 SUBOXONE 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 SUBOXONE 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 SUBOXONE sublingual film in 2 mg buprenorphine/0.5 mg naloxone, 4 mg buprenorphine/1 mg naloxone, 8 mg buprenorphine/2 mg naloxone, and 12 mg buprenorphine/3 mg naloxone strengths.

What storage and record-keeping requirements are associated with maintenance of a supply of SUBOXONE 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 SUBOXONE should keep accurate and complete records for each patient that include:

1. The medical history and physical examination
2. Diagnostic, therapeutic, and laboratory results
3. Evaluations and consultations
4. Treatment objectives
5. Discussion of risks and benefits
6. All treatments that the patient is receiving
7. Medications (including date, type, dosage, and quantity prescribed and/or dispensed to each patient)
8. A physical inventory of all Schedule III, IV, and V controlled substances on hand that are dispensed by the 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 20](#)).

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 _____
<i>Please send the completed form to:</i> 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 71-1044, 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.

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

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1-1202-021-US-0612 Printed in USA

Initiating Office-Based Opioid Therapy

Important Information for Pharmacists Frequently Asked Questions

SUBOXONE[®]

(buprenorphine and naloxone) sublingual film CIII

I. Introduction

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

This REMS does not apply to SUBOXONE film 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 SUBOXONE sublingual film?

SUBOXONE sublingual film is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

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

SUBOXONE includes a second active ingredient, naloxone HCl, at a ratio of 4:1 buprenorphine/naloxone (ratio of free bases). Naloxone is included in the SUBOXONE formulation and is intended to deter individuals from abusing it by the intravenous route.

How is SUBOXONE sublingual film different from the tablet formulation?

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

Patients being switched between SUBOXONE sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE sublingual tablets as observed in pharmacokinetic studies [see *Clinical Pharmacology* (12.3)]. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to strips or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

As indicated in [Table 1](#), the sizes and the compositions of the four units of SUBOXONE sublingual films, i.e., 2 mg/0.5 mg, 4 mg/2 mg, 8 mg/2 mg and the 12 mg/3 mg units, are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE sublingual films to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be

monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

Table 1. Comparison of available Suboxone film strengths by dimensions and drug concentrations

Suboxone film unit strength (buprenorphine/naloxone)	Suboxone film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22 mm X 19.2 mm	17.2	4.88

When is SUBOXONE prescribed?

SUBOXONE, which includes naloxone, is indicated for the maintenance treatment of opioid dependence and is preferred for unsupervised administration.

SUBUTEX[®] * (buprenorphine) sublingual tablets are preferred for use during induction. 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.

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

*SUBUTEX 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 SUBOXONE?

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

What are the goals of the REMS for SUBOXONE?

The goals of the REMS for SUBOXONE 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 SUBOXONE.

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

As part of the REMS, pharmacists dispensing SUBOXONE for opioid dependence must supply a SUBOXONE Medication Guide with each prescription. The SUBOXONE Medication Guide that accompanies the product can be found at **www.SUBOXONE.com**, and is available by calling 1-877-SUBOXONE (1-877-782-6966).

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

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

- Verify that the prescription you receive is from a physician who is in compliance with the provisions of DATA 2000
- Keep in mind that a limited supply of SUBOXONE should be dispensed during the initiation of therapy. This is due to the need of 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 SUBOXONE should be stored in a safe place to protect the medications from theft since they have the potential to be misused, diverted and abused. Unused doses of SUBOXONE 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 SUBOXONE film 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 SUBOXONE

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

Abuse Potential of SUBOXONE

Is SUBOXONE 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.

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

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, SUBOXONE may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

Can SUBOXONE cause dependence?

Buprenorphine, the active ingredient in SUBOXONE, is a partial agonist at the mu-opioid receptor. Chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. This should be considered when prescribing or dispensing buprenorphine in situations where there is 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 SUBOXONE?

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

How can patients prevent accidental exposure to SUBOXONE in children?

Patients should be instructed to keep SUBOXONE in a secure place, out of the sight and reach of children and other household members. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. If a child is exposed accidentally to SUBOXONE, seek immediate urgent medical attention.

Contraindications

- Hypersensitivity to buprenorphine or naloxone

Warnings and Precautions

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription
- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome
- Monitor liver function tests prior to initiation and during treatment, and evaluate suspected hepatic events

- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone
- A marked and intense opioid withdrawal syndrome is highly likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy
- SUBOXONE sublingual film 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 SUBOXONE?

- Adverse events commonly observed with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema
- 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 SUBOXONE for patients receiving benzodiazepines or other CNS depressants, and warn patients against concomitant self-administration/misuse

Use in Specific Populations

- SUBOXONE sublingual film 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 SUBOXONE sublingual film
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients
- Administer SUBOXONE sublingual with caution in patients with liver dysfunction

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

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

IV. Supplying and Administering SUBOXONE

How is SUBOXONE supplied?

SUBOXONE is supplied as light orange, rectangular, sublingual film with a white printed logo in a foil pouch:

- NDC 12496-1202-3 (2 mg buprenorphine + 0.5 mg naloxone/film) is printed with “N2” in white —30 films per carton
- NDC 12496-1204-3 (4 mg buprenorphine + 1 mg naloxone/film) is printed with “N4” in white – 30 films per carton
- NDC 12496-1208-3 (8 mg buprenorphine + 2 mg naloxone/film) is printed with “N8” in white —30 films per carton
- NDC 12496-1212-3 (12 mg buprenorphine + 3 mg naloxone/film) is printed with “N12” in white – 30 films per carton

How should SUBOXONE be administered?

SUBOXONE is administered sublingually.

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

V. Patient Information

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

The safety concerns related to the use of SUBOXONE include, 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 SUBOXONE. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician

- Advise patients that SUBOXONE contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place and to protect them from theft
- Instruct patients to keep SUBOXONE in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE, medical attention should be sought immediately
- Advise patients never to give SUBOXONE to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death
- Advise patients that selling or giving away SUBOXONE is against the law
- Caution patients that SUBOXONE may impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving or operating machinery. Caution should be taken, especially during drug induction and dose adjustments and until they are reasonably certain that SUBOXONE does not adversely affect their ability to engage in such activities
- Advise patients not to change the dose of SUBOXONE without consulting their physician
- Advise patients to take SUBOXONE once a day as directed
- Inform patients that SUBOXONE can cause drug dependence of the opioid type. Withdrawal signs and symptoms may occur when the medication is discontinued
- Advise patients seeking to discontinue treatment with SUBOXONE for opioid dependence to work closely with their 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, SUBOXONE may produce orthostatic hypotension in ambulatory individuals
- Ask patients if other prescription medications, over-the-counter medications or herbal preparations are prescribed or are currently being used
- Advise patients 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 SUBOXONE during pregnancy
- Warn patients that buprenorphine passes into breast milk and breast-feeding is therefore not advised in mothers treated with SUBOXONE
- 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 SUBOXONE

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

Who is qualified to prescribe SUBOXONE?

DATA 2000 limits office-based use of SUBOXONE 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 SUBOXONE?

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 SUBOXONE 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 SUBOXONE, 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 SUBOXONE 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, <http://www.hipaa.samsha.gov>, or call 1-866-BUP-CSAT (1-866-287-2728).

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

As a Schedule III controlled substance, SUBOXONE is subject to certain federal regulations covering areas such as record keeping, inventory, proper dispensing and disposal. These are explained in the DEA's Pharmacist's Manual, which can be found at www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.html. 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 SUBOXONE. 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 SUBOXONE 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 SUBOXONE. 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 SUBOXONE?

As a pharmacist, you are in a unique position to help local physicians implement office-based treatment of opioid dependence with SUBOXONE. 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 SUBOXONE, 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 SUBOXONE

- ✓ 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 SUBOXONE?

- 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 www.aaap.org.

SUBOXONE[®] is a registered trademark 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.

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

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-410/S006/S007

CHEMISTRY REVIEW(S)

Chemistry review #1	1. Division ONDQA HFD-170	2. NDA & Suppl. Number 22-410/SCE-007
3. Name and Address of Applicant Reckitt Benckiser Pharmaceuticals Inc. Attention: Clorey Toombs CMC Manager, Regulatory Affairs 10710 Midlothian Turnpike Suite 430 Richmond, VA 23235		4. DATE Submission PDUFA 9/30/11 1/30/12
5. Name of Drug: Suboxone	6. Nonproprietary Name: Buprenorphine/Nalaxone	
7. Supplement, Prior Approval, Provides for: The addition of a new strength of 12 mg/3 mg.		8. Amendment Date
9. Pharmacological Category Treatment for opioid dependence.	10. How Dispensed Rx	11. Related Documents
12. Dosage Form: Sublingual Film.	13. Potency(ies): 2 mg/0.5 mg and 8 mg/2 mg (currently approved).	
14. Comments Qualitative compositions of the proposed new strengths, 12 mg/3 mg is identical to the currently approved 8 mg/2 mg dosage but it is 1.5 times the size and weight. Manufacture, Manufacturing process and control remained the same. The primary container/closure system remained the same. Satisfactory stability data, 36 months on 6 batches stored at 25°C/60% RH, were provided. Proposed expiration dating period is (b) (4).		
15. Conclusions and Recommendations: Recommend approval.		
17. Name: Review Chemist Bart Ho, Chemist Branch Chief James D. Vidra, Ph.D.	Signature Signature	Date Date

Doc ID: 22410S07 New Strength Reckitt Benckiser

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/s/

BARTHOLOME C HO
03/08/2012

JAMES D VIDRA
03/08/2012

Chemistry review #1	1. Division ONDQA HFD-170	2. NDA & Suppl. Number 22-410/SCE-006
3. Name and Address of Applicant Reckitt Benckiser Pharmaceuticals Inc. Attention: Clorey Toombs CMC Manager, Regulatory Affairs 10710 Midlothian Turnpike Suite 430 Richmond, VA 23235		4. DATE Submission PDUFA 9/29 1/30/12
5. Name of Drug: Suboxone	6. Nonproprietary Name: Buprenorphine/Nalaxone	
7. Supplement, Prior Approval, Provides for: The addition of a new strength of 4 mg/1 mg.		8. Amendment Date
9. Pharmacological Category Treatment for opioid dependence.	10. How Dispensed Rx	11. Related Documents
12. Dosage Form: Sublingual Film	13. Potency(ies): 2 mg/0.5 mg and 8 mg/2 mg (currently approved).	
14. Comments Qualitative compositions of the proposed new strengths, 4 mg/1 mg is identical to the currently approved 2 mg/0.5 mg dosage but it is twice the size and weight. Manufacture, Manufacturing process and control remained the same. Satisfactory 3 batches data were provided. The primary container/closure system remained the same. Satisfactory stability data on three batches stored at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH were provided. Proposed expiration dating period is (b) (4)		
15. Conclusions and Recommendations: Recommend approval.		
17. Name: Review Chemist Bart Ho, Chemist Branch Chief James D. Vidra, Ph.D.	Signature Signature	Date Date

Doc ID: 22410S06 New Strength Reckitt Benckiser

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/s/

BARTHOLOME C HO
03/08/2012

JAMES D VIDRA
03/08/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-410/S006/S007

PHARMACOLOGY REVIEW(S)



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

MEMO TO FILE

PHARMACOLOGY TOXICOLOGY

NDA number: 22410
Serial #; date: 006 (SDN 138 submit date 9/29/11 received date 9/30/11) and 007 (SDN 139 submit and received date 9/30/11)
Drug: Suboxone Sublingual Film
Indication: Treatment of opioid dependence
Sponsor: Reckitt Benckiser Pharmaceuticals, Inc.
Date of Memo: March 8, 2012

Reviewer name: Elizabeth A. Bolan, Ph.D.
Division name: Division of Anesthesia, Analgesia, and Addiction Products
HFD #: 170

Background

Suboxone Sublingual Film (NDA 22410) was approved on August 30, 2010. This product is designed to deliver buprenorphine by the sublingual and buccal routes and is marketed as an alternative to Suboxone Sublingual Tablets (NDA 20733), which are also owned by Reckitt Benckiser. Naloxone is included in both Suboxone formulations to deter misuse by injection. Dosage strengths in the original 22410 application were 2 mg/0.5 mg and 8 mg/2 mg buprenorphine/naloxone combinations. Supplements 006 and 007 seek to add the additional dosage strengths of 4 mg/1 mg and 12 mg/3 mg buprenorphine/naloxone. Supplements 006 and 007 contain updated drug product specifications for the Suboxone Film (b) (4) product. With (b) (4), the specifications are identical to those approved in NDA 22410. This memo serves to document that the (b) (4) for (b) (4) is below the ICH Q3B(R2) threshold for qualification and is considered acceptable from the pharmacology/toxicology perspective.

(b) (4) is a naloxone-derived degradant and does not contain any structural alerts for mutagenicity. The qualification threshold according to the ICH Q3B(R2) guidelines for impurities/degradants in the drug product for a maximum daily dose (MDD) of <10 mg administered per day is 1% or 50 mcg TDI, whichever is lower. The MDD for the naloxone component of Suboxone Sublingual (b) (4) is (b) (4) mg. With (b) (4)

(b) (4) (b) (4) (b) (4) impurities in Suboxone Film (b) (4) are identical to those approved in the original NDA (Table 1). The stability specification proposed by the Applicant of (b) (4) % for (b) (4) is below the ICH Q3B(R2) threshold for qualification for a MDD of naloxone of (b) (4) mg and is considered acceptable from the pharmacology/toxicology perspective.

Table 1	Stability Specifications of Suboxone (b) (4) drug product impurities/degradants for Supplements 006 and 007		
Source	Impurity/degradant	Stability specification limit	Acceptable?
buprenorphine	(b) (4)	NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
naloxone		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
		NMT (b) (4)	YES
NMT (b) (4)	YES		

* impurity has been qualified (see discussion in NDA 22410 review dated 5/22/09 by Dr. Elizabeth Bolan)

Recommendation

The stability specification proposed by the Applicant of (b) (4) % for (b) (4) in the Suboxone Film (b) (4) product is considered acceptable. From the nonclinical pharmacology/toxicology perspective, supplements 006 and 007 for NDA 22410 can be approved.

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/s/

ELIZABETH BOLAN
03/09/2012

RICHARD D MELLON
03/09/2012
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-410/S006/S007

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

<i>NDA</i>	22-410 S006 and S007	<i>Submission Date(s)</i>	Nov 1, 2011
<i>Brand Name</i>	Suboxone (b) (4)		
<i>Generic Name</i>	Buprenorphine (bup) and Naloxone (nal)		
<i>Reviewer</i>	Sheetal Agarwal, Ph.D.		
<i>Team Leader</i>	Yun Xu, Ph.D.		
<i>OCP Division</i>	Division of Clinical Pharmacology-2		
<i>OND Division</i>	Division of Anesthesia, Analgesia, and Addiction Products		
<i>Sponsor</i>	Reckitt Benckiser Pharmaceuticals Inc.		
<i>Submission Type</i>	CMC Supplements		
<i>Formulation; Strength(s)</i>	Sublingual film strips; 4 mg bup/1 mg nal and 12 mg bup/3 mg nal		
<i>Indication</i>	Maintenance treatment of opioid dependence		
<i>Proposed Dosing Regimen</i>	Recommended target dose for maintenance is 16 mg bup/4 mg nal per day		

RECOMMENDATION:

Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 has reviewed Reckitt Benckiser's CMC supplements requesting approval of 4/1 mg and 12/3 mg Suboxone SL film (b) (4) and finds both the new strengths acceptable from a Clinical Pharmacology perspective.

We note that the exposures of both buprenorphine and naloxone from the 12/3 Suboxone SL film (b) (4) are higher as compared to the reference Suboxone tablets that are already approved and in the market. However, a safety study RB-US-07-0001 employing the 12/3 mg strips up to the labeled dose of currently marketed Suboxone, i.e. up to 24/6 mg, was reviewed at the time of the original NDA 22-410 submission and provides acceptable safety data for the 12/3 mg strips.

Also, based on various PK studies that have been reviewed for this product, we note that exposure of buprenorphine and naloxone from a single 12/3 mg strip may be different from a combination of 8/2 and 2/0.5 mg strips at the same nominal dose. This can result in over or under dosing of Suboxone in clinical setting when patients switch between one 12/3 or a combination of the currently approved 8/2 and 2/0.5 mg strengths to obtain the same nominal dose. To warn health care practitioners regarding over or under dosing of Suboxone, the sponsor has included adequate labeling language addressing this issue in their new proposed label.

BACKGROUND:

The sponsor, Reckitt Benckiser, is seeking approval of 2 new strengths of Suboxone sublingual film (b) (4) i.e. 4/1 and 12/3 mg under CMC supplements for NDA 22-410 (original NDA approved on Aug 30, 2010). Currently, the sponsor is marketing 2/0.5 and 8/2 mg strengths for

both Suboxone (buprenorphine: naloxone in 4:1 ratio) strips as well as Suboxone tablets under approved NDAs 22-410 (approved by referencing NDA 20-733) and 20-733, approved on October 8, 2002, respectively. Currently, Suboxone dosing is approved up to 24/6 mg as a maintenance dose (based on the label).

DATA PROVIDED IN SUPPORT OF APPROVAL OF 4/1 STRENGTH:

In support of the 4/1 mg Suboxone SL film (b) (4) the sponsor has provided the following:

- a. Reference to relative BA study (study 20-272-SA) employing 2 of the 2/0.5 mg strips in the original NDA: This study was reviewed and found to be acceptable in the original NDA. See Clinical Pharmacology original NDA review in DARRTS dated 06/23/2009. This study showed that the Suboxone film (b) (4) when administered as 2 X 2/0.5 mg (4/1 mg dose) are bioequivalent with respect to rate and extent of absorption, of both buprenorphine and naloxone to the reference product, 2 X 2/0.5 Suboxone tablets.
- b. Qualitative composition of the 4/1 mg strip indicating that it is compositionally proportional to the currently marketed 2/1 mg Suboxone SL film (b) (4)

Reviewer's comments: No clinical or clinical pharmacology study was conducted using the 4/1 mg strip. The 4/1 mg strip is simply double the size of the currently approved and marketed 2/0.5 mg Suboxone SL film (b) (4) and study 20-272-SA showed that 2 X 2/0.5 mg strips are BE with respect to buprenorphine and naloxone exposure to reference Suboxone tablets. Although the sponsor did not explicitly ask for a biowaiver in the submission, since the sponsor is not conducting any clinical studies with this strength, a biowaiver was needed to approve this strength. In Dr. Deepika Lakhani's review for NDA 22-410/supplements 6 and 7 (dated 03/07/2012 in DARRTS), the ONDQA/Biopharm review team has determined that a biowaiver can be granted to the 4/1 mg strip as it is compositionally proportional to the 2/0.5 mg strip. As such, the 4/1 mg strip is acceptable from a Clinical Pharmacology perspective.

DATA PROVIDED IN SUPPORT OF APPROVAL OF 12/3 STRENGTH:

In support of the 12/3 mg Suboxone SL film (b) (4) the sponsor has provided the following:

- a. Reference to relative BA studies (studies 20-B20-AU and 1003395): These studies have also been reviewed at the time of the original NDA 22-410 submission (Dr. Sheetal Agarwal's clinical pharmacology review in DARRTS dated 06/23/2009). Study 1003395 showed that when administered as a combination of one 8/2 mg and two 2/0.5 mg strips (12/3 mg total dose), the strips met the bioequivalent criteria with respect to rate and extent of absorption of buprenorphine, and with respect to extent of absorption of naloxone to the reference product, Suboxone tablets administered as one 8/2 and two 2/0.5 mg tablets (see Table 1 below). Study 20-B20-AU showed that the 12/3 mg strips (single strength strip) are not bioequivalent to Suboxone tablets (one 8/2 and two 2/0.5 mg tablets) with respect to buprenorphine or naloxone (see Table 2 below).
- b. Reference to safety data from study RB-US-07-0001 that was also reviewed at the time of the original NDA submission (Dr. Celia Winchell's clinical review in DARRTS dated 08/20/2010). This study included up to 12 weeks of safety data in subjects receiving up to 32/8 mg of Suboxone using Suboxone (b) (4). The sponsor was asked to provide data indicating how many subjects in this study were dosed with the final to-be-marketed 12/3 mg strip and the sponsor indicated that up to 57 subjects in this study received the 12/3

mg strip for a dose up to 24/6 mg. Since the safety data for study RB-US-07-0001 was found to be acceptable in the original NDA review, we can expect that the higher buprenorphine or naloxone exposures from the 12/3 mg strength of the Suboxone (b) (4) will not pose any safety concern.

- c. Qualitative composition of the 12/3 mg strip indicating that it is simply 1.5 times the size of the currently marketed 8/2 mg Suboxone SL film (b) (4)

Table 1: PK Parameters and Confidence Intervals for Buprenorphine and Naloxone after Sublingual Administration of Reference Suboxone® Tablets (one of 8/2 mg and two of 2/0.5 mg) and Test Suboxone (b) (4) (one of 8/2 mg and two of 2/0.5 mg) in Study 1003395

		SL tab 1 of 8/2 mg + 2 of 2/0.5 mg	SL strip 1 of 8/2 mg + 2 of 2/0.5 mg	Geometric Estimate	90% Confidence Interval
	Bup Cmax (ng/mL)	3.44 (1.53)	4.05 (2.63)	115.05	106.44 – 124.35
	Bup AUC inf (ng*h/mL)	37.11 (14.14)	40.50 (15.93)	111.21	105.62 – 117.09
	Nal Cmax (pg/mL)	170.0 (77.6)	207.0 (143.0)	117.24	106.80 – 128.71
	Nal AUC inf (pg*h/mL)	524.0 (253.6)	582.7 (324.9)	110.47	102.90 – 118.60

Table 2: PK Parameters and Confidence Intervals for Buprenorphine and Naloxone after Sublingual Administration of Reference Suboxone® Tablets (one of 8/2 mg and two of 2/0.5 mg) and Test Suboxone (b) (4) (one of 16/4 mg) in Study 20-B20-AU

		SL tab	SL strip	Geometric Estimate	90% Confidence Interval
	Bup Cmax (ng/mL)	3.12 (1.33)	4.55 (2.50)	143.49	127.99-160.86
	Bup AUC inf (ng*h/mL)	33.77 (12.52)	42.06 (14.64)	127.34	115.36- 140.57
	Nal Cmax (pg/mL)	152 (92.8)	238 (144)	162.94	139.82-189.88
	Nal AUC inf (pg*h/mL)	469.3 (209.3)	653.1 (308.5)	143.41	126.79-162.20

Table 3: Revised Confidence Intervals for Buprenorphine and Naloxone after Sublingual Administration of Reference Suboxone® Tablets (one of 8/2 mg and two of 2/0.5 mg) and Test Suboxone (b) (4) (one of 16/4 mg) in Study 20-B20-AU After Excluding Subjects 201, 233, and 245

Buprenorphine:							
Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
Buprenorphine: Sublingual Film vs. Suboxone							
ln(C _{max})	4.0219	2.8030	143.49	127.99	160.86	0.9416	31.84
ln(AUC _{last})	37.1433	28.8780	128.62	115.95	142.67	0.9703	28.75
ln(AUC _{inf})	39.0721	30.6823	127.34	115.36	140.57	0.9798	27.36
Buprenorphine: Sublingual Film vs. Suboxone Excluding Subjects 201, 233, and 245							
ln(C _{max})	3.9794	2.9052	136.98	122.93	152.63	0.9594	28.72
ln(AUC _{last})	37.5120	30.9968	121.02	110.92	132.04	0.9938	22.98
ln(AUC _{inf})	39.4256	32.8387	120.06	110.53	130.41	0.9965	21.78

Naloxone:							
Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
Naloxone: Sublingual Film vs. Suboxone							
ln(C _{max})	202.1484	124.0621	162.94	139.82	189.88	0.7777	43.46
ln(AUC _{last})	553.8698	371.2201	149.20	131.62	169.14	0.9015	35.11
ln(AUC _{inf})	589.3570	410.9694	143.41	126.79	162.20	0.9106	31.52
Naloxone: Sublingual Film vs. Suboxone Excluding Subjects 201, 233, and 245							
ln(C _{max})	200.0983	127.2542	157.24	133.75	184.86	0.7371	44.04
ln(AUC _{last})	564.1098	388.3596	145.25	127.10	166.00	0.8678	35.82
ln(AUC _{inf})	620.0829	445.4263	139.21	122.51	158.19	0.8923	31.45

Reviewer's comments: Based on studies 1003395 and 20-B20-AU, although exposure of buprenorphine and naloxone is very similar between the strips and the tablets when administered as a combination of one 8/2 and two 2/0.5 strips (total nominal dose of 12/3 mg); the 12/3 mg strip is not bioequivalent to the same combination of tablets with respect to buprenorphine or naloxone. The 12/3 mg strip may show higher exposures of buprenorphine and naloxone as compared to a combination of the 8/2 and the 2/0.5 mg strips administered at the same nominal dose.

As indicated by the sponsor, the marked differences in exposures of buprenorphine from the 12/3 mg strips as compared to the tablets in study 20-B20-AU are mitigated when 3 subjects who experienced emesis during the study (all 3 subjects received reference Suboxone tablets) are removed from the PK analysis as shown below in Table 3. The log-transformed C_{max}, AUC_{last}, and AUC_{inf} of buprenorphine for the 12/3 mg strip formulation were approximately 43%, 29%, and 27% higher, respectively, than the values after administration of reference Suboxone tablets with all subjects included. After excluding Subjects 201, 233, and 245 (who

experienced emesis after drug administration); the log-transformed C_{max}, AUC_{last}, and AUC_{inf} of buprenorphine for the 12/3 mg strip were approximately 37%, 21%, and 20% higher, respectively, than the values after administration of reference Suboxone tablets. Similar magnitude of decreases in naloxone exposures even after exclusion of those 3 subjects were not observed (see Table 3 below). However, the 12/3 mg strips can still not be considered bioequivalent to the reference Suboxone tablets.

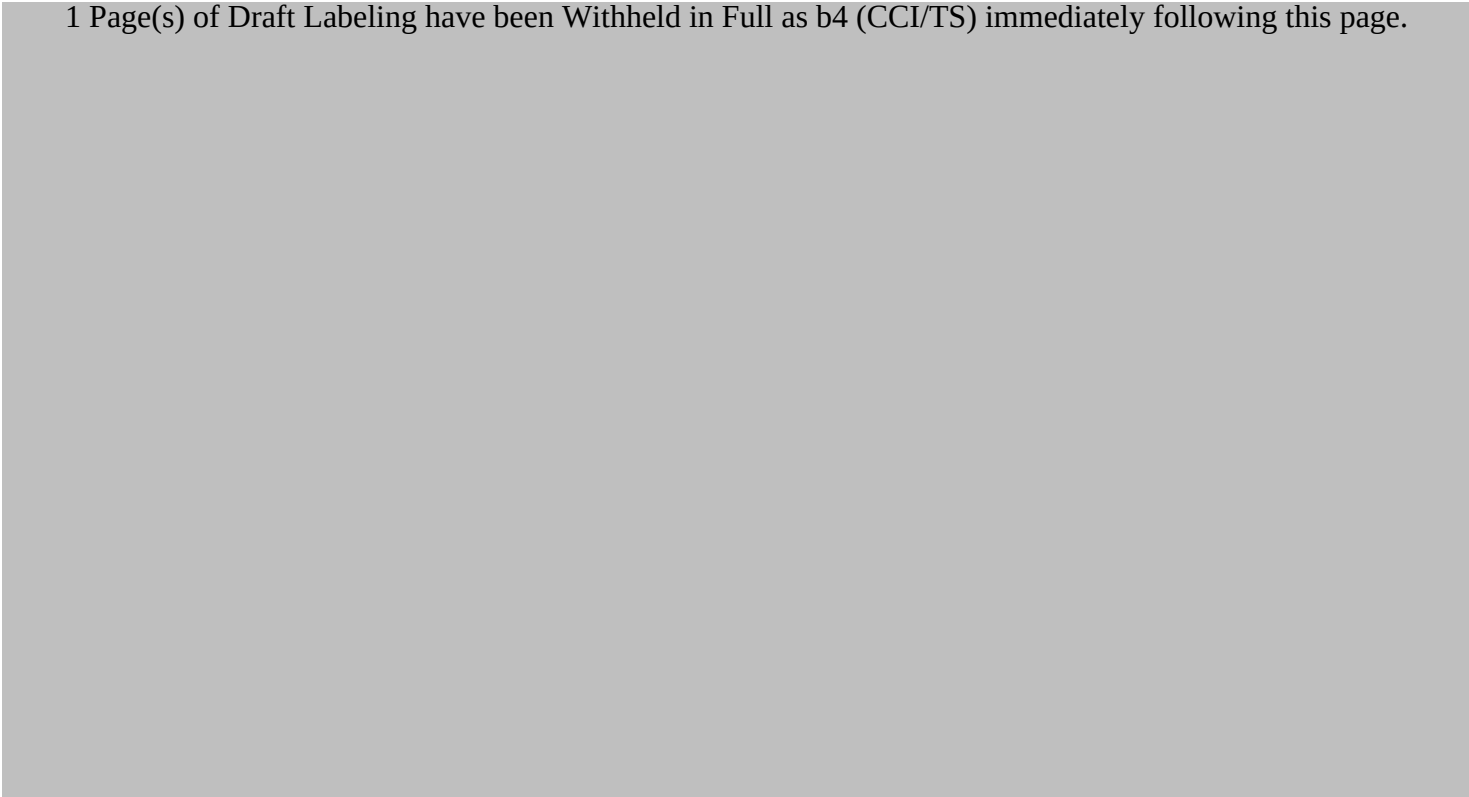
In spite of higher exposure of buprenorphine and naloxone from the 12/3 mg strip, it can be considered acceptable for approval based on the following reason. As determined by the clinical review team (Dr. Pamela Horn's clinical review in DARRTS dated 03/08/2012), the 12/3 mg strips do not pose any additional safety concerns as compared to what was already determined for the 8/2 strips as they are simply 1.5 times the size of the approved 8/2 mg strips that were found to be safe based on a safety study (study RB-US-07-0001) employing these strips at the time of the original NDA submission (Dr. Celia Winchell's clinical review in DARRTS dated 08/20/2010). As such, we consider the 12/3 mg strips acceptable from a Clinical Pharmacology perspective.

LABELING:

Since it is possible that the 12/3 mg strips perform differently as compared to a combination of the 8/2 mg and 2/0.5 mg strips in a clinical setting in terms of buprenorphine and naloxone exposures, it is important this phenomenon be clearly explained to the health practitioners through product labeling. As mentioned in the Recommendation section above, the sponsor has adequately addressed this issue in the product labeling as indicated below:

Section 2.6 Switching between SUBOXONE Sublingual Tablets and SUBOXONE Sublingual Film

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.



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/s/

SHEETAL S AGARWAL
03/08/2012

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03/08/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.	NDA 22-410/S-006 and S-007	Reviewer	Deepika Arora Lakhani, Ph.D
Division	CDER/Div of Metabolism & Endocrinology Products		
Sponsor	Reckitt Benckiser Pharmaceuticals	Team Leader	Angelica Dorantes, Ph.D.
Trade Name	SUBOXONE Sublingual film	Acting Supervisor	Angelica Dorantes, Ph.D.
Generic Name	buprenorphine HCl/naloxone HCl dihydrate	Date Assigned	Nov 14, 2011
Indication	Treatment of opiod dependence	Date of Review	Mar 02, 2012
Formulation	Sublingual films (2/0.5 mg and 8/2.0 mg buprenorphine/nalaxone)		
Route of Administration	Sublingual		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Date	CDER Stamp Date	Date of Informal/ Formal Consult	Internal Meeting
S-006: Sep 29, 2012 S-007: Sep 30, 2012	S-006: Sep 29, 2012 S-007: Sep 30, 2012		NA
Type of Submission	Prior-Approval Supplements		
Type of Consult	Review of the dissolution profile data supporting a biowaiver for the proposed 4 mg/1mg buprenorphine and naloxone dosage strength		
REVIEW SUMMARY: The approved dosage strengths under this NDA are the 2mg/0.5 mg buprenorphine and naloxone and 8mg/2mg buprenorphine and naloxone combinations. In these two PAS, the Applicant is seeking the addition of the following 2 new strengths: ▪ S-006: 4 mg/1mg buprenorphine and naloxone dosage strength ▪ S-007: 12 mg/3mg buprenorphine and naloxone dosage strength The proposed 12/3 mg strength was used in a PK study as well as a clinical efficacy study (both reviewed in NDA 22-410); however, the 4/1 strength has not been used in any clinical study. For the 4/1 dosage strength, the reviewer requested the Applicant to submit additional information to support the biowaiver for the proposed 4/1 mg strip with an approved strength of the same strip using f2 matrix dissolution data generated with the approved dissolution method. The dissolution data presented supports the similarity of the 4/1 dosage strength with the approved 2/0.5mg film strips			
RECOMMENDATION: ONDQA-Biopharmaceutics has evaluated the dissolution profiles provided in the application for the Suboxone sublingual film. The data provided in the supplement show similar dissolution behavior for the 4/1 mg strip vs. the approved 2/0.5 mg strip. Therefore, a BA waiver is granted for the 4 mg/1mg buprenorphine and naloxone dosage strength. From the Biopharmaceutics perspective, NDA 22-410/S-006 and S-007 for SUBOXONE Sublingual Films are recommended for APPROVAL.			
Deepika Arora Lakhani, Ph. D. CMC/Biopharmaceutics Reviewer Office of New Drug Quality Assessment		Angelica Dorantes, Ph. D. Acting Biopharmaceutics Supervisor Office of New Drug Quality Assessment	

BIOPHARMACEUTICS ASSESSMENT**INTRODUCTION**

- These two PAS (S-006 and 007) under NDA 22-410, proposes the addition of 2 new strengths (4 mg/1mg and 12 mg/3mg buprenorphine and naloxone strengths under S-006 and S-007, respectively).
- The 12 mg/3mg buprenorphine and naloxone dosage strength have supportive PK study as well as a clinical efficacy study (both reviewed in NDA 22-410); however, the 4/1 strength has not been used in any clinical study. Hence, the Applicant was contacted to submit additional information to support the similarity or the proposed 4/1 mg strip with an approved strength of the same strip using f2 matrix dissolution data generated with the approved dissolution method. These dissolution profile comparison and f2 data were needed to support a bioavailability (BA) waiver for this new strength.

DISSOLUTION SUPPORTING DATA

No change is reported in the dissolution testing methodology or the acceptance criteria.

DISSOLUTION PROFILES

Identical dissolution testing was performed for three Suboxone 4mg / 1mg sublingual film batches (D11HF101-119, D11HF102-122 and D11HF103-123) and the approved dosage strength 2mg / 0.5mg sublingual film strip as the reference batches. The dissolution profiles were compared at 3 and 5 minutes dissolution in addition to the registered 7 minutes.

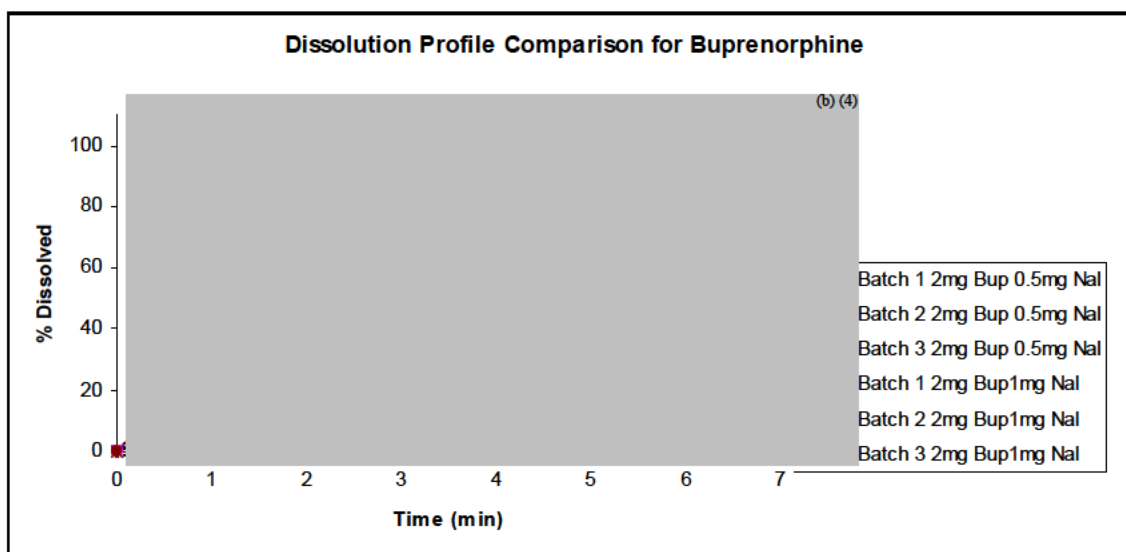


Figure 1. Average Dissolution Profile Comparison for Buprenorphine between the approved Suboxone 2/0.5 mg strip and proposed Suboxone 2/1 mg strip

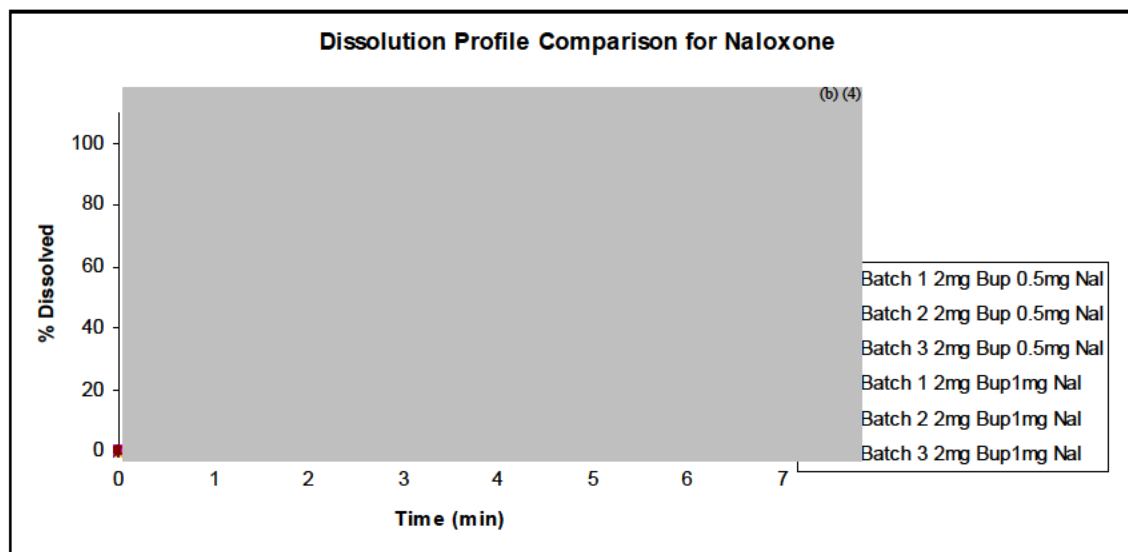


Figure 2. Average Dissolution Profile Comparison for Naloxone between the approved Suboxone 2/0.5 mg strip and proposed Suboxone 2/1 mg strip

SIMILARITY FACTOR CALCULATION

The dissolution profiles above show that more than (b) (4)% of the drug dissolves within the first time point measurement (3 mins) for all strips and both strengths. Therefore, the calculation of f2 similarity factor is not possible and f2 values do not need to be reported.

RECOMMENDATION

- The comparison of the dissolution results for Suboxone sublingual film in support of the proposed 4/1 mg film strip versus the approved 2/0.5 mg strip support the similarity of the products. Therefore, a waiver for the CFR requirement to provide in vivo BA data for the newly proposed 4 mg/1mg buprenorphine and naloxone dosage strength is granted.
- From the Biopharmaceutics point of view the proposed NDA 22-410/S-006 and S-007 for SUBOXONE Sublingual Films are recommended for APPROVAL.

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/s/

DEEPIKA LAKHANI

03/06/2012

Recommend Approval from Biopharmaceutics perspective.

ANGELICA DORANTES

03/07/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-410/S006/S007

OTHER REVIEW(S)

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Date: July 19, 2012

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products
(DAAAP)

Through: Claudia B. Manzo, PharmD, Director
Division of Risk Management (DRISK)

From: Mary Dempsey, BS, Risk Management Programs Coordinator, DRISK
Kate Heinrich Oswell, MA, Health Communications Analyst, DRISK
Kim Lehrfeld, PharmD, Risk Management Analyst, DRISK

Subject: Prior Approval Supplement (PAS); REMS modification

Drug Name: Suboxone (buprenorphine and nalaxone) sublingual film (b) (4)

Application

Type/ Number: NDA 022410/S006 and S/007

Applicant/Sponsor: Reckitt Benckiser Pharmaceuticals, Inc.

OSE RCM #: 2012-364

1 Background and Introduction

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review the Suboxone (buprenorphine and naloxone) sublingual film (b) (4) proposed Risk Evaluation Mitigation Strategy (REMS) Modification for the New Drug Application (NDA) 022410 submitted by Reckitt Benckiser Pharmaceuticals, Inc. for S/006 and S/007. These are supplements that propose to provide two additional strengths of Suboxone and are being reviewed under separate cover by the following Offices/Divisions: Chemistry is reviewing the new dosage strengths, Division of Medication Error Prevention Analysis (DMEPA) is reviewing carton and containers, and Division of Medical Policy Programs (DMPP) is reviewing the Medication Guide. The focus of this review is the REMS modification which proposed to incorporate two new dosage strengths in the REMS materials. The Medication Guide, which is part of the REMS, is being reviewed under separate cover by the Division of Medical Policy Programs (DMPP) Patient Labeling Team.

The initial Suboxone film (b) (4) REMS was approved August 28, 2010 with the following elements:

- Medication Guide
- Elements to Assure Safe Use
 - REMS Instruction Letter to Prescribers
 - Physician Brochure- Important Information for Physicians- Frequently Asked Questions
 - Appropriate Use Checklist
 - REMS introductory Letter to Pharmacists
 - Pharmacists Brochure- Important Information for Pharmacists- Frequently Asked Questions
- Implementation System
- Timetable for Submission of Assessments

2 Material Reviewed

- August 30, 2010 initial REMS approval
- September 29, 2011 (S006) REMS modification to include 4mg/1mg buprenorphine/naloxone strength
- September 30, 2011 (S007) REMS modification to include 12mg/3mg buprenorphine/naloxone strength
- January 27, 2012 (S006) Amendment to REMS modification
- January 30, 2012 (S007) Amendment to REMS modification
- June 4, 2012 (S006) Amendment to REMS modification
- June 4, 2012 (S007) Amendment to REMS modification

3 Proposed REMS Elements

The applicant, Reckitt Benckiser Pharmaceuticals, Inc., submitted proposed REMS modifications to include two new dosage strengths as follows:

- September 29, 2011 (S006) REMS modification to include 4mg/1mg buprenorphine/naloxone strength
- September 30, 2011 (S007) REMS modification to include 12mg/3mg buprenorphine/naloxone strength

The REMS and all REMS materials should include the text from both submissions and all amendments submitted to S006 and S007.

The proposed revisions are to include the addition of the new dosage strengths to the following sections of the REMS materials:

- Important Information for Pharmacists-Frequently Asked Questions

How is SUBOXONE sublingual film different from the tablet formulation?
Supplying and Administering SUBOXONE

- Important Information for Physicians- Frequently Asked Questions

How is SUBOXONE sublingual film different from the tablet formulation?
How do I get SUBOXONE for use in the office?

4 Discussion and Conclusion

There were multiple discussions and emails between DAAAP and the applicant that resulted in the following additional revisions to the REMS materials:

- 1) text regarding substitution of dosage strengths

“For this reason, pharmacists should not substitute one or more strengths for another without approval of the prescriber.”

- 2) a table with Suboxone film strengths by dimensions and drug concentrations

Table 1. Comparison of available Suboxone film strengths by dimensions and drug concentrations

Suboxone film unit strength (buprenorphine/naloxone)	Suboxone film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2mg/0.5mg	22.0 mm x 12.8 mm	5.4	1.53
4mg/1mg (2 times the length of the 2mg/0.5mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8mg/2mg	22.0 mm x 12.8 mm	17.2	4.88
12mg/3mg (1.5 times the length of the 8mg/2mg unit)	22 mm x 19.2 mm	17.2	4.88

3) removal of the text regarding product disposal

“Instruct patients to dispose of unused doses of Suboxone film by flushing the films down the toilet.”

5. Recommendation

DRISK compared the August 30, 2010 approved REMS to the proposed REMS for S006 and S007 and find the revisions consistent with the inclusion of the two new dosage strengths as well as the other revisions outlined in this review.

The proposed REMS document contains (b) (4) in table format and that should be removed.

The REMS document and REMS materials, with the exception of the Medication Guide, are attached and acceptable.

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/s/

MARY J DEMPSEY
07/19/2012

CLAUDIA B MANZO
07/23/2012
concur

Division of Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 022410/S-006
NDA 022410/S-007

Name of Drug: Suboxone (buprenorphine and naloxone) sublingual film

Applicant: Reckitt Benckiser Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: (S006) September 29, 2011, June 4, 2012 (final)
(S007) September 30, 2011, June 4, 2012 (final)

Receipt Date: (S006) September 30, 2011, June 4, 2012
(S007) September 30, 2011, June 4, 2012

Background and Summary Description:

Reckitt Benckiser Pharmaceuticals, Inc. submitted a Prior Approval supplement (PAS) to add 4mg/1mg (buprenorphine/naloxone) strength (S/006) and 12 mg/3 mg (buprenorphine/naloxone) strength (S/007). Currently, strengths: 2mg/0.5 mg and 8mg/2 mg of buprenorphine and naloxone combination are approved. The proposed content of labeling includes both strengths.

The last approved label for NDA 022410 was under original application approved on August 30, 2010. This was compared to the final label submitted on June 4, 2012 to the pending supplements.

Review

Additions to the last approved labeling are shown in underline text, while deletions are shown in strikeout.

Refer to the Division of Medication Error Prevention and Analysis (DMEPA) review in DARRTS dated March 26, 2012 which contained the following comments:

A. Insert Labeling

a. Highlights of Prescribing Information

i. Dosage and Administration reads “The recommended daily dose for maintenance is 16/4 mg.” We recommend this statement be revised to read “The recommended daily dose for maintenance is buprenorphine and naloxone 16 mg/4 mg”. As currently presented it is not clear that both active ingredients are represented in the presentation of the recommended dose. **(Concurred)**

ii. Dosage and Administration. We recommend adding the statement “Advice patients not to cut, chew or swallow the sublingual films.” **(Concurred)**

b. Full Prescribing Information

i. We note that throughout the PI the strength of the products does not include the units next to each strength component (e.g. 4/1 mg, or 24/6 mg). USP guidelines recommend that the strength of combination products be presented as XX mg/XX mg. We recommend that the presentation of strength throughout the PI be revised so that each component includes the “mg” units (e.g. 4 mg/1 mg, or 24 mg/ mg). **(Concurred)**

ii. Method of Administration (Section 2.2). We recommend revising the statement that reads “Suboxone sublingual film should NOT be chewed, swallowed or moved after placement” to read “Suboxone sublingual film should NOT be cut, chewed, swallowed or moved after placement”. **(Concurred)**

iii. Patient Counseling Information (Section 17). We adding the statement “Patients should be advised NOT to cut, chew or swallow the sublingual films.” **(Concurred)**

HIGHLIGHTS OF PRESCRIBING INFORMATION:

Following changes were noted under DOSAGE AND ADMINISTRATION

-----DOSAGE AND ADMINISTRATION-----

Administer SUBOXONE sublingual film sublingually as a single daily dose. (2)

The recommended daily dose for maintenance treatment is ~~16/4mg~~ 16mg/4mg buprenorphine and naloxone. Advise patients not to cut, chew, or swallow SUBOXONE sublingual film.

Following changes were noted under DOSAGE FORMS AND STRENGTHS

-----DOSAGE FORMS AND STRENGTHS-----

Sublingual film: 2 mg buprenorphine with 0.5 mg naloxone ~~and , 4 mg~~ buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone. (3)

RPM Comment: Addition of 4mg/1mg (buprenorphine/naloxone) strength is provided for in S-006, whereas addition of 12mg/3mg (buprenorphine/naloxone) strength is provided for in S-007.

Following change was noted for Sec. 17 Heading:

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

RPM Comment: Added required statement per Selected Requirements of Prescribing Information (SRPI) format review tool.

FULL PRESCRIBING INFORMATION: **CONTENTS:**

Following changes were noted in Sec. 2 and Sec. 17 of the table of content:

- 2 **DOSAGE AND ADMINISTRATION**
- 2.1 Maintenance

- 2.2 Method of Administration
- 2.3 Clinical Supervision
- 2.4 Unstable Patients
- 2.5 Stopping Treatment
- 2.6 Switching between SUBOXONE (~~buprenorphine and naloxone~~) Sublingual Tablets and SUBOXONE Sublingual Film
- 2.7 Switching between different strengths of SUBOXONE Sublingual Film

17 PATIENT COUNSELING INFORMATION

- 17.1 Safe Use
- ~~17.2 Disposal of Unused SUBOXONE Sublingual Film~~

RPM Comment: Sec. 2.7 is added to provide instruction on switching between two strengths. Sec. 17.2 is deleted per revised Agency guidelines on medications which should not be disposed of via flushing.

BOX WARNING: Not Applicable

FULL PRESCRIBING INFORMATION:

- 1 **INDICATIONS AND USAGE:** No changes noted
- 2 **DOSAGE AND ADMINISTRATION:** Following changes were noted
 - 2.2 **Method of Administration**

Do not cut, chew, or swallow SUBOXONE sublingual film. Place a ~~SUBOXONE~~ sublingual film under the tongue. If an additional sublingual film is necessary to achieve the prescribed dose, place an additional sublingual film sublingually on the opposite side from the first film. Place the sublingual film in a manner to minimize overlapping as much as possible. The sublingual film must be kept under the tongue until the film is completely dissolved. ~~SUBOXONE sublingual film should NOT be chewed, swallowed, or moved after placement.~~ **SUBOXONE sublingual film should NOT be moved after placement. Proper administration technique should be demonstrated to the patient**

- 2.6 **Switching between SUBOXONE (~~buprenorphine and naloxone~~) Sublingual Tablets and SUBOXONE Sublingual Film**

~~Patients being switched between SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Because of the potentially greater relative bioavailability of SUBOXONE sublingual film compared to SUBOXONE (buprenorphine and naloxone) sublingual tablets, patients switching from SUBOXONE (buprenorphine and naloxone) sublingual tablets to SUBOXONE sublingual film should be monitored for over medication. Those switching from SUBOXONE sublingual film to SUBOXONE (buprenorphine and naloxone) sublingual tablets should be monitored for withdrawal or other indications of under dosing. In clinical studies, pharmacokinetics of SUBOXONE sublingual film was similar to the respective dosage strengths of SUBOXONE (buprenorphine and naloxone) sublingual tablets, although not all doses and dose combinations met bioequivalence criteria.~~

Patients being switched between SUBOXONE sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE sublingual tablets as observed in pharmacokinetic studies [see Clinical Pharmacology (12.3)]. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to strips or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

2.7 Switching between SUBOXONE Sublingual Film strengths

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

Table 1. Comparison of available Suboxone film strengths by dimension and drug concentrations

<u>Suboxone film unit strength (buprenorphine/naloxone)</u>	<u>Suboxone film unit dimensions</u>	<u>Buprenorphine Concentration % (w/w)</u>	<u>Naloxone Concentration % (w/w)</u>
<u>2 mg/ 0.5mg</u>	<u>22.0 mm x 12.8mm</u>	<u>5.4</u>	<u>1.53</u>
<u>4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)</u>	<u>22.0 mm x 25.6 mm</u>	<u>5.4</u>	<u>1.53</u>
<u>8 mg/ 2 mg</u>	<u>22.0 mm x 12.8 mm</u>	<u>17.2</u>	<u>4.88</u>
<u>12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)</u>		<u>17.2</u>	<u>4.88</u>

RPM Comment: Due to differences in the bioavailability between different strengths and with the addition of two new strengths to the SUBOXONE sublingual film family, instructions on switching between 2 different strengths or between different dosage form (tablets and sublingual film) prevents confusion and avoids potential medication errors (overdose or under dose).

3 **DOSAGE FORMS AND STRENGTHS:** Following changes were noted:

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in ~~two~~four dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg, ~~and~~
- buprenorphine/naloxone ~~8~~4 mg/~~2~~1 mg.,
- buprenorphine/naloxone 8 mg/2 mg, and
- buprenorphine/naloxone 12 mg/3 mg

RPM Comment: The change reflects addition of two new strengths.

4 CONTRAINDICATIONS: No changes noted

5 WARNINGS AND PRECAUTIONS: Following changes were noted in sec. 5.4

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children ~~and destroy any unused medication appropriately. [see Disposal of Unused SUBOXONE Sublingual Film (17.2)].~~

RPM Comment: Acceptable

6 ADVERSE REACTIONS: No changes noted

7 DRUG INTERACTIONS: No changes noted

8 USE IN SPECIFIC POPULATIONS: No changes noted

9 DRUG ABUSE AND DEPENDENCE: No changes noted

10 OVERDOSAGE: No Changes noted

11 DESCRIPTION: Following changes were noted in 1st paragraph

SUBOXONE (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual administration and is available in ~~two~~four dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone ~~and, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone~~. Each sublingual film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

RPM Comment: Change reflects addition of new strengths

12 CLINICAL PHARMACOLOGY: Following Changes were noted in 12.3

12.3 Pharmacokinetics

Absorption

Table 3 shows the pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after administration of SUBOXONE sublingual film in randomized, crossover studies. The pharmacokinetics of the SUBOXONE sublingual film is similar to the pharmacokinetics of the respective dosage strengths of Suboxone (buprenorphine/naloxone) sublingual tablets, although not all doses and dose combinations met bioequivalence criteria.

Table 3 Pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after the sublingual administration of SUBOXONE sublingual film

Dose	Analyte	Mean SD	C _{max} (ng/mL)	T _{max} (h)	AUC _{inf} (h•ng/mL)	t _{1/2} (h)
2 mg/ 0.5 mg	Buprenorphine	Mean SD	0.947 0.374	1.72 0.60	8.654 2.854	33.41 13.01
	Norbuprenorphine	Mean SD	0.312 0.140	2.26 2.03	14.52 5.776	56.09 31.14
	Naloxone*	Mean SD	54.1 23.0	0.77 0.26	137.3 43.10	5.00 5.52
8 mg/ 2 mg	Buprenorphine	Mean SD	3.37 1.80	1.53 0.66	30.45 13.03	32.82 9.81
	Norbuprenorphine	Mean SD	1.40 1.08	2.17 2.63	54.91 36.01	41.96 17.92
	Naloxone*	Mean SD	193 91.2	0.81 0.19	480.8 201.0	6.25 3.14

*Naloxone C_{max} expressed as pg/mL. Naloxone AUC_{inf} expressed as h•pg/mL

In pharmacokinetic studies, the 2mg/0.5mg and 4mg/1mg doses administered as SUBOXONE sublingual films showed comparable relative bioavailability to the same nominal dose of SUBOXONE sublingual tablets, whereas the 8mg/2 mg and 12mg/3mg doses administered as SUBOXONE sublingual films showed higher relative bioavailability compared to the same nominal dose of SUBOXONE sublingual tablets. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE sublingual films showed comparable relative bioavailability to the same nominal dose of SUBOXONE sublingual tablets [See Dosage and Administration (2.6 and 2.7)].

RPM Comment: Based on the clinpharm review by Dr. Sheetal Agarwal, (see DARRTS review dated 3/8/2012) the applicant has clearly explained the health practitioners difference in performance of Suboxone film and tablets of different strengths in clinical settings and the changes are acceptable to the reviewer.

13 NONCLINICAL TOXICOLOGY: No changes noted

16 HOW SUPPLIED / STORAGE AND HANDLING: Following changes noted

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine/naloxone 2 mg/0.5 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1204-3 (buprenorphine/naloxone 4 mg/1 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine/naloxone 8 mg/2 mg/film; content expressed in terms of free base) -30 films per carton
- NDC 12496-1212-3 (buprenorphine/naloxone 12 mg/3 mg/film; content expressed in terms of free base) - 30 films per carton

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children. ~~Destroy any unused medication appropriately [see Disposal of Unused SUBOXONE Sublingual Film (17.2)].~~

RPM Comment: Addition of NDC number is due to addition of two new strengths and is acceptable.

17 PATIENT COUNSELING INFORMATION: Following changes were noted

See FDA-approved patient labeling (Medication Guide)

Patients should be advised NOT to cut, chew or swallow SUBOXONE sublingual film.

17.1 Safe Use: No Changes noted

~~17.2—Disposal of Unused SUBOXONE Sublingual Film~~

~~Unopened SUBOXONE sublingual films should be disposed of as soon as they are no longer needed:~~

- ~~1. Remove the SUBOXONE film from its foil pouch.~~
- ~~2. Drop the SUBOXONE film into the toilet.~~
- ~~3. Repeat steps 1 and 2 for each SUBOXONE film. Flush the toilet after all unneeded films have been put into the toilet.~~

~~Foil pouches or cartons should not be flushed down the toilet.~~

RPM Comment: Sec. 17.2 is deleted per revised Agency guidelines on medications which should not be disposed of via flushing.

MEDICATION GUIDE

Refer to review dated 3/12/12 in DARRTS from Division of Medical Policy Programs (DMPP). They did not recommend any changes to the Medication Guide.

However based on changes to the PI during labeling negotiations, the following section was removed from the MG

~~How should I dispose of unused SUBOXONE sublingual film?~~

- ~~• Dispose of unopened SUBOXONE sublingual films as soon as you no longer need them:~~
 - ~~1. Remove the SUBOXONE film from its foil pouch.~~
 - ~~2. Drop the SUBOXONE film into the toilet.~~
 - ~~3. Repeat steps 1 and 2 for each SUBOXONE film. Flush the toilet after all unneeded films have been put into the toilet.~~
- ~~• Do not flush foil pouches or cartons down the toilet.~~

RPM comments: Sec. 17.2 of the PI was deleted per revised Agency guidelines on medications which should not be disposed of via flushing. Therefore the MG was updated as well.

CARTON AND CONTAINER

Refer to the Division of Medication Error Prevention and Analysis (DMEPA) review in DARRTS dated March 26, 2012:

A. Pouch Labels (Proposed strengths: 4 mg/1 mg, 12 mg/3 mg)

Revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.

B. Pouch Labels (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)

At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.

C. Carton Labeling (Proposed strengths: 4 mg/1 mg, 12 mg/3 mg)

Revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.

D. Carton Labeling (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)

At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.

The applicant moved the “Do not cut, chew or swallow sublingual film” to the Principal Display Panel for the 4mg/ 1mg and the 12mg/ 3mg pouch and carton. A reminder will be included in the AP letter to revise the other labeling at the next printing.

Recommendations

The PI, MG and carton and pouch labels are acceptable.

Concurrence

Matthew Sullivan, Sr. RHPM
Sara Stradley, CPMS
Pamela Horn, Medical Officer
Celia Winchell, Clinical TL

8/8/2012
7/27/12
7/31/12
7/31/12

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

/s/

MATTHEW W SULLIVAN
08/08/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: March 26, 2012

Reviewer(s): Carlos M Mena-Grillasca, RPh, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Lubna Merchant, MS, PharmD
Division of Medication Error Prevention and Analysis

Deputy Director: Kellie Taylor, PharmD, MPH
Division of Medication Error Prevention and Analysis

Drug Name(s) and Strength(s): Suboxone (Buprenorphine and Naloxone) Sublingual Films
2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg

Application Type/Number: NDA 022410

Submission Number: S-006 and S-007

Applicant/sponsor: Reckitt Benckiser Pharmaceuticals, Inc.

OSE RCM #: 2012-577

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed pouch labels, carton, and insert labeling for Suboxone NDA 022410 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Sponsor is proposing two new strengths to the Suboxone sublingual film product line. Currently Suboxone is marketed in two dosage forms; sublingual tablets and sublingual films. Both dosage forms are marketed in the same two strengths; 2 mg/0.5 mg and 8 mg/2 mg.

Reckitt Benckiser Pharmaceutical submitted Supplement S-006 for the introduction of a 4 mg/1 mg sublingual film and Supplement S-007 for the introduction of a 12 mg/3 mg sublingual film.

1.2 REGULATORY HISTORY

Suboxone sublingual tablets (NDA020733) was approved on October 8, 2002. Suboxone sublingual films (NDA 022410) was approved on August 30, 2010.

Both formulations of Suboxone are marketed under a Risk Evaluation and Mitigation Strategy (REMS). The goals of the REMS is to mitigate the risks of accidental overdose, misuse and abuse, and to inform patients of the serious risks associated with Suboxone. The elements of the REMS include: (a) Medication Guide, (b) Elements to Assure Safe Use: Safe use conditions and Monitoring, (c) Implementation System, and (d) Timetable for Submission of Assessments.

In addition, prescription use of Suboxone in the treatment of opioid dependence is limited under the Drug Addiction Treatment Act to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services 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.

1.3 PRODUCT INFORMATION

The following product information is provided in the Suboxone sublingual film submission.

- **Active Ingredient:** Buprenorphine and Naloxone
- **Indication of Use:** Maintenance treatment of opioid dependence and should be part of a complete plan to include counseling and psychosocial support.
- **Route of Administration:** Sublingual
- **Dosage Form:** Sublingual Film
- **Strength:** Currently marketed: 2 mg/0.5 mg and 8 mg/2 mg
Proposed: 4 mg/1 mg and 12 mg/3 mg
- **Dose and Frequency:**
 - Recommended target dose of Suboxone is 16 mg/4 mg as a single daily dose.
 - The dose should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

- The maintenance dose is generally in the range of 4 mg/1 mg to 24 mg/6 mg per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage.
- **How Supplied:** Cartons of 30 pouches; One film per pouch
- **Storage:** 25°C (77 °F), excursions permitted to 15-30 °C (59-86 °F).
- **Container Closure System:** Child-resistant polyester/foil laminated pouches

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Suboxone sublingual film medication error reports. We also reviewed the Suboxone labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date of Search	March 9, 2012
Drug Names	Verbatim Terms: "Subo%" Trade name: "Suboxo%"
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (PT)
Time Limitation	2/1/2009 (last AERS search in a Suboxone review 2008-1807) to 3/9/2012

The AERS database searches identified 148 reports. Each report was reviewed for relevancy and duplication. After individual review, 123 reports were not included in the final analysis for the following reasons:

- Reports related to the sublingual tablet formulation
- Accidental exposure
- AE not related to a medication error
- Intentional underdose or overdose
- Intentional wrong route of administration (i.e. intravenous) for the purpose of abuse
- Lack of effect
- Product complaint

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Pouch Labels submitted September 30, 2011 (Appendix B)
- Carton Labeling submitted September 30, 2011 (Appendix C)
- Carton Labeling for the approved Suboxone Sublingual Tablets from DailyMed (Appendix D)
- Insert Labeling submitted January 27, 2012

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the labels and labeling for Suboxone sublingual films in OSE review 2008-1807, dated July 1, 2009. Subsequently, DMEPA reviewed the final labels and labeling for Suboxone sublingual films in OSE review 2009-2346, dated April 20, 2010 where we found the labels acceptable.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our AERS search and the risk assessment of the Suboxone sublingual film product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

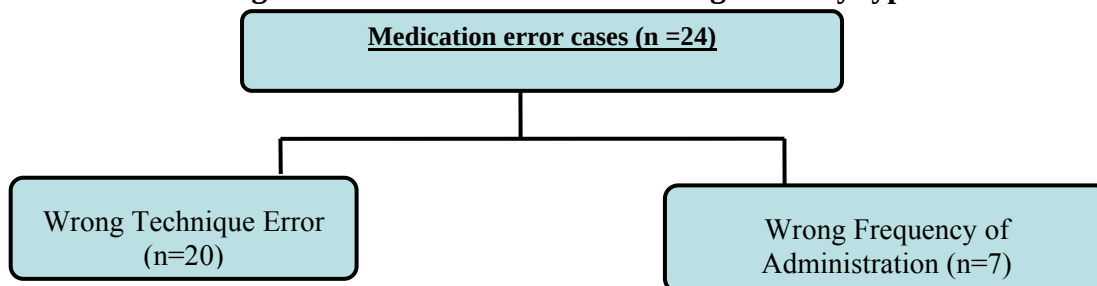
Following exclusions as described in section 2.1, 24 Suboxone sublingual films medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter². Figure 1 provides a stratification of the number of cases included in the review by type of error. We note that the number of medication error types (n=27) is higher than the number of AERS cases (n=24) because 3 cases reported more than one error, hence the discrepancy.

Appendix E provides listings of all ISR numbers for the cases summarized in this review. Table 2 in Appendix 4 contains a more detailed listing of the cases.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>. Accessed June 1, 2011.

Figure 1: Suboxone Sublingual Films medication errors categorized by type of error



3.1.1 Wrong Frequency of Administration (n=7)

We identified 7 cases where Suboxone doses ranging from 4 mg to 8 mg were taken twice to four times daily. All the cases suggest that the doses were prescribed, although patients taking more than their prescribed dose was also mentioned in at least one of the cases. Outcomes included withdrawal symptoms, visit to the Emergency Room, and Hospitalization. However, causality for the cases of Hospitalization and ER visit was not established.

All the total daily doses were within the maximum recommended dose of 24 mg daily (with the exception of one dose at 32 mg). We reviewed the Prescribing Information and noted that it clearly indicates that the recommended doses are administered as a single daily dose.

3.1.2 Wrong Technique (n=20)

We identified 20 cases of wrong technique in the administration of the Suboxone film.

One case reported that the film sticks to her teeth and the patient is unsure if she is getting the complete dose and takes another film. Outcome reported in the case include suicidal thoughts and tiredness. The second case reported that the patient in placing the film on top of the tongue and that is hard for her not to swallow the film. However, a follow up report indicates that the patient is doing better with the film now. The report states that placing the film on top of the tongue was physician prescribed. The outcome reported in the case includes pneumonia and “sick to the stomach”. We note that the Prescribing Information and Medication Guide clearly indicate how to place the film under the tongue.

The remaining 18 cases report patients cutting the film either to achieve their prescribed doses, to reduce the doses, or to self taper their doses. A few cases indicate that the patients were cutting the film per physicians instructions to achieve their doses. Outcomes include visits to the ER (n=2), Hospitalizations (n=7), cravings and anxiety (n=1), placenta previa (n=1), withdrawal symptoms (n=2), death (n=1, cause known), swelling of extremities and rash (n=1), suicidal thoughts (n=1), nausea and dizziness (n=1), headaches (n=1), pneumonia and “sick to stomach” (n=1), and unknown (n=1). However, it is difficult to establish causality of the outcomes and whether they were related to the errors described in the report.

3.2 INTEGRATED SUMMARY OF MEDICATION ERROR AND LABELS AND LABELING RISK ASSESMENT

We reviewed the Prescribing Information, Medication Guide, and pouch label and carton labeling and noted that although there are clear instructions indicating not to chew or swallow the film, there is no mention of not cutting the film. In addition, we note that the film has no markings to provide for precise and adequate cutting.

The introduction of two additional strengths to the Suboxone sublingual film product line should help minimize the practice of cutting films to achieve doses not currently available with the strengths that are currently approved.

The pouch labels and carton labeling for the proposed strengths follow the currently approved labels and labeling previously found adequate by DMEPA. We evaluated if the color scheme proposed for the new strengths adequately differentiate all four strengths and found it acceptable. In addition, we evaluated whether the proposed strengths are consistent with the Dosage and Administration of the approved labeling and found it acceptable.

4 CONCLUSIONS

DMEPA concludes that the proposed strengths are consistent with the product's dosage and administration and not likely to introduce new types of errors with Suboxone film. The proposed pouch labels and carton labeling are well differentiated but that these labels and the insert labeling can be improved to clarify that the films should not be cut.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of these Supplements:

5.1 COMMENTS TO THE REVIEW DIVISION

A. Insert Labeling

a. Highlights of Prescribing Information

- i. Dosage and Administration reads “The recommended daily dose for maintenance is 16/4 mg.” We recommend this statement be revised to read “The recommended daily dose for maintenance is buprenorphine and naloxone 16 mg/4 mg”. As currently presented it is not clear that both active ingredients are represented in the presentation of the recommended dose.
- ii. Dosage and Administration. We recommend adding the statement “Advice patients not to cut, chew or swallow the sublingual films.”

b. Full Prescribing Information

- i. We note that throughout the PI the strength of the products does not include the units next to each strength component (e.g. 4/1 mg, or 24/6 mg). USP guidelines recommend that the strength of combination products be presented as XX mg/XX mg. We recommend that the presentation of strength throughout the PI be revised so that each component includes the “mg” units (e.g. 4 mg/1 mg, or 24 mg/ mg).
- ii. Method of Administration (Section 2.2). We recommend revising the statement that reads “Suboxone sublingual film should NOT be chewed, swallowed or moved after placement” to read “Suboxone sublingual film should NOT be cut, chewed, swallowed or moved after placement”.
- iii. Patient Counseling Information (Section 17). We adding the statement “Patients should be advised NOT to cut, chew or swallow the sublingual films.”

5.2 COMMENTS TO THE SPONSOR

- A. Pouch Labels (Proposed strengths: 4 mg/1 mg, 12 mg/3 mg)
 - a. Revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.
- B. Pouch Labels (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)
 - a. At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.
- C. Carton Labeling (Proposed strengths: 4 mg/1 mg, 12 mg/3 mg)
 - a. Revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.
- D. Carton Labeling (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)
 - a. At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.

If you have further questions or need clarifications, please contact Danyal Choudhry, project manager, at 301-796-3813.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Proposed Pouch Labels

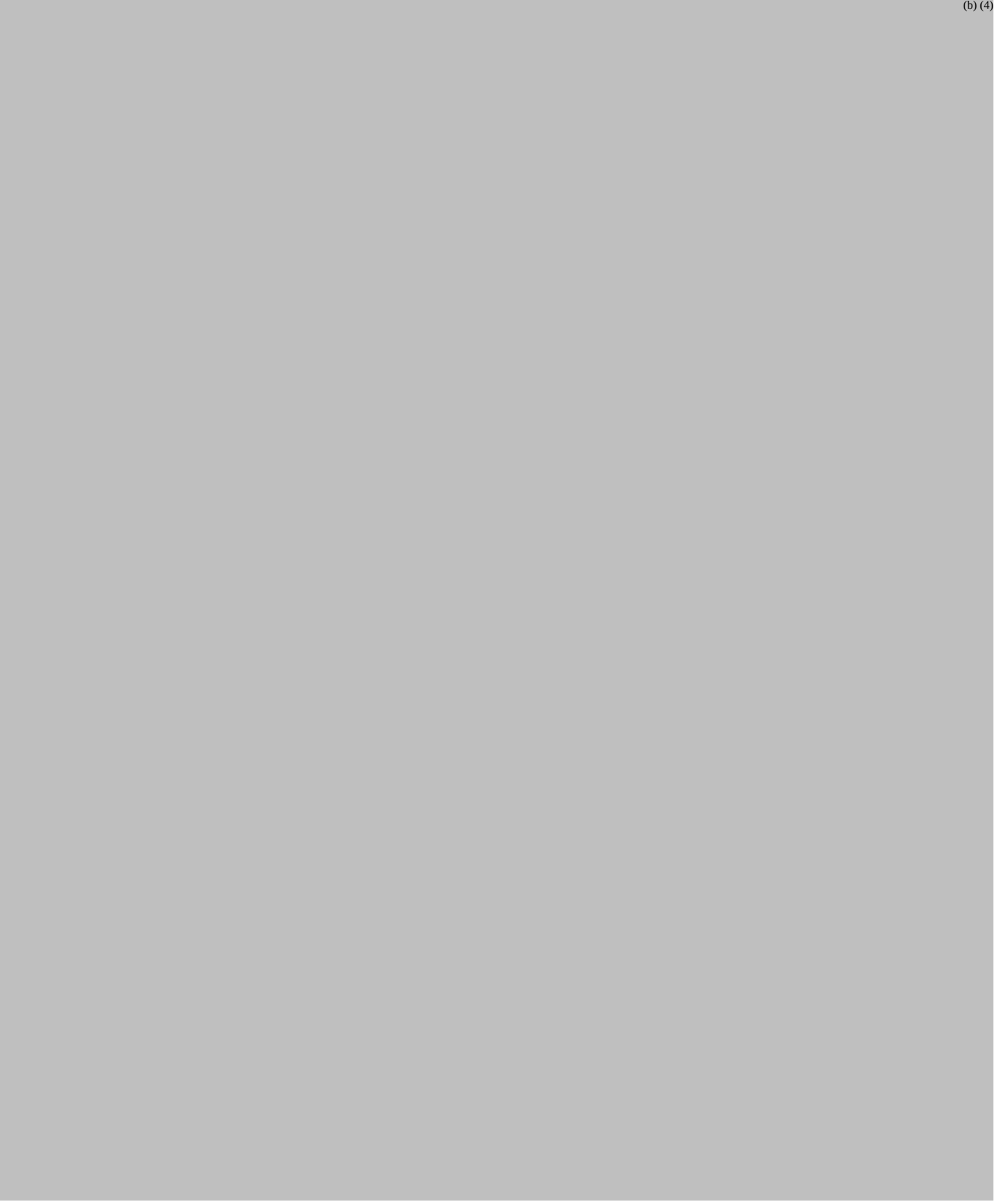
(b) (4)

Currently Marketed Pouch Labels

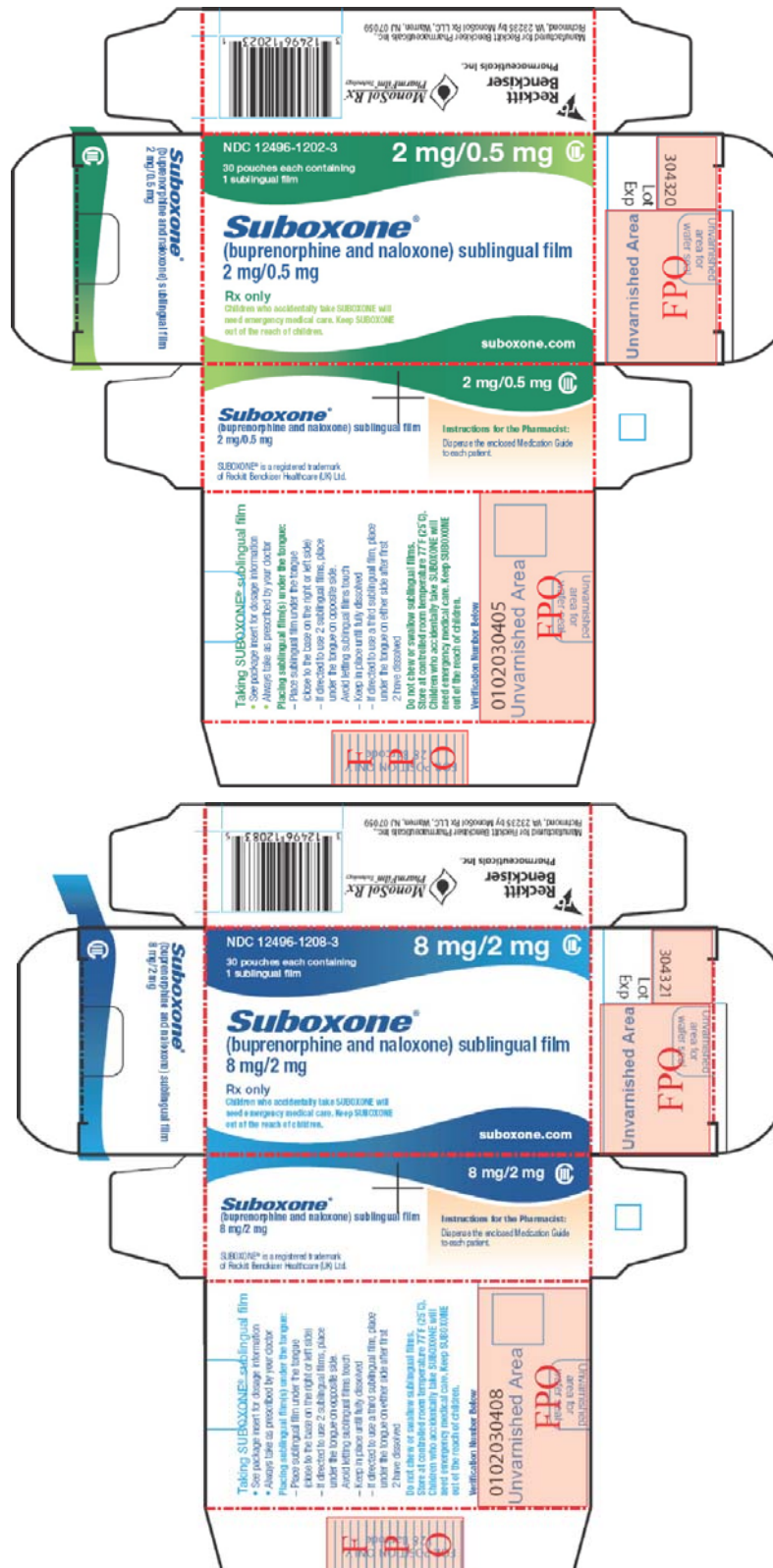


Appendix C: Proposed Carton Labeling

(b) (4)



Currently Marketed Carton Labeling



Appendix D: Currently Marketed Container Labels for Suboxone Sublingual Tablets

Usual Dose: See Product Information.
Store at 25°C (77°F) (see insert).
Mfd. by: Reckitt Benckiser Healthcare (UK) Ltd., Hull, HU8 7DS, UK.
Dist. by: Reckitt Benckiser Pharm. Inc. Richmond, VA 23235.

NDC 12496-1283-2 30 Tablets Rx only

Suboxone®
(buprenorphine and naloxone) sublingual tablets

2 mg / 0.5 mg

Pharmacist: Dispense the accompanying Medication Guide to each patient. Children who accidentally take SUBOXONE will need emergency medical care. Keep SUBOXONE out of the reach of children.

3 12496 12832 9

LOT
EXP.
RB2160

Usual Dose: See Product Information.
Store at 25°C (77°F) (see insert).
Mfd. by: Reckitt Benckiser Healthcare (UK) Ltd., Hull, HU8 7DS, UK.
Dist. by: Reckitt Benckiser Pharm. Inc. Richmond, VA 23235.

NDC 12496-1306-2 30 Tablets Rx only

Suboxone®
(buprenorphine and naloxone) sublingual tablets

8 mg / 2 mg

Pharmacist: Dispense the accompanying Medication Guide to each patient. Children who accidentally take SUBOXONE will need emergency medical care. Keep SUBOXONE out of the reach of children.

3 12496 13062 9

LOT
EXP.
RB2158

Appendix E: Details of Medication Error Cases Retrieved from AERS involving Suboxone Sublingual Films

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7398374-5, 4/6/2011, unk/male (US)	Wrong frequency of administration	Knowledge deficit	Withdrawal symptoms and suicidal thoughts.	Patient was taking Suboxone film mg three times daily. He began taking more than prescribed. Dose was increased to 8 mg four times daily. The patient abruptly discontinued Suboxone film and developed withdrawal and suicidal thoughts.
7413827-9, 4/13/2011, 53 y.o./male (US)	Wrong technique	Knowledge deficit	Pneumonia, sick to stomach.	Patient reports that Suboxone film seems less powerful than the Suboxone tablet. He is taking the film on top of his tongue, which is physician prescribed. Patient also reports that the Suboxone film is hard for him not to swallow. When he swallowed it, he got terribly sick to his stomach. Patient reports he is doing better with the film now and it is working fine for him.
8020499-1, 1/3/12, 58 y.o./male (US)	Wrong technique	Knowledge deficit	ER visit due to difficulty breathing (Diagnosed with congestive heart failure)	Patient began taking Suboxone tablets 4 mg three times daily. He continued cutting the film as he was prescribed to do with the tablets to achieve his daily dose (cutting tablets and film as prescribed. Concomitant medications include Neurontin for chronic pain, Celexa for his history of depression and Trazadone to help him sleep at night.
8057402-4, 1/19/12, 40 y.o./male (US)	Wrong technique	Knowledge deficit	Hospitalization (Diagnosed with gallbladder disease; gallbladder was removed).	Patient was switched to the film 8 mg daily on an unknown date. On an unspecified date in 2011 his Suboxone Film dose was decreased to 4 mg daily. He was cutting the film to achieve this dose.
7349335-3, 3/14/11, 30 y.o./male (US)	Wrong frequency of administration	Knowledge deficit	Hospitalization due to suicide attempt	Patient was treated with Suboxone film 8 mg twice daily. On an unknown date in Feb/2011 he stopped taking Suboxone and experienced withdrawal symptoms. On (b) (4) the patient attempted to commit suicide by taking an overdose of pills. Concomitant medications include Celexa and Trazodone.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7692455-4, 8/18/11, 61 y.o./male (US)	Wrong frequency of administration	Knowledge deficit	“Panicky feeling, difficulty remembering things, and not feeling like himself”	Patient was diagnosed with liver cancer. He received chemotherapy and opiate medication as part of his treatment and then started Suboxone film 8 mg three times a day. He started to have panicky feeling, difficulty remembering things, and not feeling like himself. These adverse events lasted about 2 weeks before resolving on JUN-2011. On JUL-2011, Suboxone film 8 mg was decreased to twice a day.
7612379-8, 7/16/11, 31 y.o./female (US)	Wrong frequency of administration Wrong technique	Knowledge deficit	Withdrawal symptoms	On JAN-2011 the patient was switched to Suboxone film, taking 4 mg four times a day. On JAN-2011 she began cutting strips to achieve dose. CS has a history of endometriosis, and on APR-2011 she was diagnosed with increased endometriosis and had laparoscopic laser surgery for removal. On APR-2011 dose decreased to 12-16 mg daily and CS began to experience periodic withdrawal symptoms, she feels this adverse event may be related to Suboxone film use, it is an on-going event.
7673045-6, 8/9/11, 38 y.o./female (US)	Wrong technique	Knowledge deficit	Cravings and anxiety.	A 38 year old female, reports she is currently seven weeks pregnant with a high risk pregnancy due to a previous diagnosis of: Von Willebrand disease. She is bleeding/hemorrhaging and clotting. She receives Factor eight hormone shots to clot while on Suboxone Film and Subutex. While on Subutex she was anxious and had cravings which are now resolved. She now breaks/cuts/splits film into six pieces. The patient started Suboxone Film daily 8 mg daily on 2010 for opioid type dependence.
8014893-2, 12/29/11, 28 y.o./female (US)	Wrong technique	Knowledge deficit	Placenta previa	On 23-Jun-2011 the consumer started taking 12 mg Suboxone film per day, (taking one and half films per day). She had placenta previa which began in 2011 and on (b) (4) she gave birth to a female baby weighing 5 pounds 10 ounces via Cesarean section. The physician's causality changed from possible to unrelated in relation to placenta previa and Suboxone.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7732535-8, 9/6/11, 33 y.o./male (US)	Wrong technique	Knowledge deficit	Hospitalization due to Xanax overdose.	A 33 year old male, began taking Suboxone Film (details unknown) for his opioid type dependence. He had been cutting the film without physician's guidance. He was also obtaining illicit Xanax, "you could see his eyes change" clarified as high, beginning on an unknown date. He had changes in respiration, clarified as wheezing. He was taken to the hospital where he blacked out clarified as lost consciousness. He was hospitalized for two nights and was then transferred to a 28 day detox center. Patient has a long history of multiple substance abuse including alcohol and gambling addiction.
8057406-1, 1/19/2012, 61 y.o./male (US)	Wrong technique DUPLICATE	Knowledge deficit	Headache and nausea	Patient was switched to the Suboxone film on Jun-2011 and immediately began to "radically reduce his dose on his own". The patient was able to do this by cutting the film. During the tapering process he developed headaches and nausea.
7813295-9, 10/13/11, 40 y.o./female (US)	Wrong technique	Knowledge deficit	Withdrawal and hallucinations	Patient started Suboxone Film 10 mg daily on May-2011 for opioid type dependence. She is cutting the Film. Reporter causality is possible for withdrawal and hallucinations.
7953210-0, 12/1/11, 55 y.o./male (US)	Wrong technique	Knowledge deficit	Death	A 55 year old male, began taking Suboxone film 6 mg daily on Jan-2011 for opioid type dependence. He died unexpectedly on (b) (4). The cause of death is unknown. The patient was cutting the film to achieve his dose. Concomitant medications included an unspecified antihypertensive. Reporter causality is possible.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7980780-9, 12/14/11, 61 y.o./male (US)	Wrong frequency of administration Wrong technique	Knowledge deficit	Hospitalization due to intestinal blockage.	In 2010, a male patient started treatment with Suboxone film 8 mg three times a day for opioid-type dependence. On an unknown date, his dose was reduced to 8 mg twice a day and then to 8 mg daily. In 2011, he started cutting the film strip to achieve a self-tapering dose of 6 mg daily. Also in 2011, he was admitted to the hospital and an x-ray indicated an intestinal blockage. He recovered and was discharged from hospital after 5 days. The patient resumed Suboxone film 2 mg but again began to self-taper the dose and resumed cutting film strips to achieve this. His physician agreed at this time to taper the dose of Suboxone with him. At the time of this report, he was cutting a 2 mg film strip in order to take 1/4 mg twice a day.
7968901-5, 12/9/11, unk./female (US)	Wrong technique	Knowledge deficit	Hospitalization due to severe cough and respiratory condition.	A female taking Suboxone 12 mg daily (cutting the 8 mg film) for her OTD experienced a severe cough on Aug-2011. She passed out after coughing for a long period and was hospitalized for two days. She has a pre-existing history of asthma, bronchitis and COPD for which she uses combivent and symbicort inhalers daily. She was treated in the hospital with oxygen and respiratory treatments. These events have resolved.
8120716-3, 2/7/12, unk./female (US)	Wrong technique	Knowledge deficit	Swelling of extremities and rash	A female of unknown age commenced treatment with Suboxone film at a dose of 24 mg daily in Aug-2011 for opioid-type dependence. On an unknown date, the patient began cutting film strips, in order to cut her dose down to 4 mg daily. In Aug-2011 the patient developed swelling of extremities which then developed into a reddened rash. Her reporter considered the events of abdominal pain, benign mass, blockage and infection to be unrelated to Suboxone treatment, and the remaining adverse events of swelling of extremities, rash, withdrawal and cutting film to be related to Suboxone treatment.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7333536-4, 3/4/11, 37 y.o./female (US)	Wrong technique	Performance deficit	Suicidal thoughts, tiredness	Patient began taking Suboxone tablets and film 24 mg daily prescribed from a physician on Nov-2010 for opioid type dependence. She uses the medication interchangeably to make 24 mg daily dose. She had suicidal thoughts for a couple of days (dates unknown) due to the stress in her life, which is resolved. While on Suboxone Sublingual Film, reports she sometimes takes another film strip because "sometimes the film sticks to the back of my teeth" and she isn't sure she "got it all". She also states she feels tired halfway through the day.
7648927-1, 8/1/11, 56 y.o./female (US)	Wrong technique	Knowledge deficit	Nausea and dizziness	On an unspecified date on 2011 the patient was switched from Suboxone tablets to Suboxone film. On JUN-2011 she began to experience nausea and feeling woozy and she started to taper her Suboxone dose. She is cutting film strips in order to do so. Concomitant medication includes Wellbutrin for depression.
7784956-5, 9/28/11, 65 y.o./male (US)	Wrong technique	Knowledge deficit	Hospitalization for a stent	The patient was switched to the Film 2-3 mg daily on Jul-2011. He cuts the Film. He developed blockage of renal artery on an unknown date, was hospitalized in Aug-2011 for a stent. He stopped the Suboxone Film 2-3 days before having the stent placed. He was hospitalized overnight for the procedure. He was given Versed and Fentanyl during the procedure. After the procedure he developed nausea and vomiting. This resolved after one day.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7962949-2, 12/7/11, unk./female (US)	Wrong technique	Knowledge deficit	Emergency room visit for visual and auditory hallucinations	A 55 year old female started Suboxone Film 20 mg daily on 28-Jul-2011 for opioid type dependence. She used Suboxone film for induction. SL also was cutting the 8 mg Suboxone film. SL's dose was increased to 24 mg daily on 23-Aug-2011 and she began to have auditory and visual hallucinations on (b) (4). The patient was seen in the emergency room for the visual and auditory hallucinations, and was given Geodon as treatment. The auditory and visual hallucinations are now resolved. Patient was advised to cut down his dose of Suboxone film (no further clarification given). Concomitant medication included ibuprofen, clomipramine, buspirone, dextansoprazole, citalopram, atenolol, methocarbamol and meclizine.
8139969-0, 2/15/12, 47 y.o./male (US)	Wrong technique	Knowledge deficit	Hospitalization due to stomach problems (i.e. stomach mucosal atrophy)	Patient reports switching to the Suboxone film 16 mg daily on 28-Mar-2011, which he is cutting without physician's direction. He reports his nausea has resolved following this switch. He now is experiencing an increased appetite. He has recently begun working out and feels increased appetite may be related to this activity. He has been prescribed Thorazine which he states is taken daily for his nausea since an unknown date in 2010. He started Lisinopril 20 mg daily on Jul-2011 and developed nausea on Aug-2011 which is ongoing. On an unspecified date in Oct-2011 the patient's stomach problems worsened, he experienced a butterfly rash of the face, joint problems, increased blood pressure and an increased heart rate. Upon these events he was hospitalised for three days. Investigations during hospitalisation included an oesophagogastroduodenoscopy which confirmed the previous diagnosis of stomach mucosal atrophy.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7761550-3, 9/20/11, 33 y.o./female (US)	Wrong frequency of administration Wrong technique	Knowledge deficit	Vomiting, diarrhea, suicidal thoughts, headaches, withdrawal symptoms	A 33 year old female started Suboxone 8 mg twice daily on 02-Sep-2011 for opioid type dependence. (b) (4) used the Film for induction. Immediately after taking the first dose of 8 mg she developed vomiting and diarrhea. These both resolved on 02-Sep-2011. She also developed "suicidal depression" and headaches on 02-Sep-2011. She took 8 mg twice daily for two days, took 8 mg for one day (04-Sep-2011) and cut the Suboxone Film into a 4 mg piece for one day (05-Sep-2011) and then stopped the Suboxone on 05-Sep-2011. She developed withdrawal on 06-Sep-2011. The Suicidal depression, headaches and withdrawal resolved on 06-Sep-2011 when (b) (4) restarted her hydrocodone.
8074683-1, 1/26/12, 61 y.o./male (US)	Wrong technique	Knowledge deficit	Unknown	The consumer had a long medical history of opioid dependence, and commenced treatment with Suboxone film at a dose of 16-24 mg daily on 01-Feb-2011. Concomitant medications included antihypertensives (brand name, dosage, route and frequency were not provided). In 2011 he was stopped his Suboxone and was prescribed oxycodone during this treatment period for his increased pain. The patient restarted Suboxone on 18-Jan-2012, not as prescribed, taking 8-12 mg daily. He was cutting film strips in order to achieve his dose. He had been noncompliant with his medical treatment and follow-ups, and did not take his prescribed medications as ordered.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
7645957-0, 7/29/11, 28 y.o./male (US)	Wrong technique	Knowledge deficit	Hospitalization due to arrhythmia. Withdrawal symptoms during suboxone dose tapering.	A 28 year old male, was switched to Suboxone 8 mg Film in late 2010. He had no adverse effects while on the Tablets. On FEB-2011 he began to taper his dose down to 2 mg. On (b) (4) he reports he developed nausea, felt shaky, and he felt like his heart was racing. He went to the Emergency Room for evaluation. An EKG revealed the arrhythmia bigeminy so he was admitted to the hospital for additional testing. He had an angiogram, and echocardiogram which showed no blockage, but his Ejection Fraction was 30%. He was put on Coreg, Zestril, and Amiodarone for the arrhythmia. He was discharged on (b) (4) but returned on (b) (4) due to shortness of breath that developed that day. He was once again discharged on (b) (4). The nausea resolved on 27-MAR-2011, the shakiness, heart racing, and shortness of breath resolved on ??-APR-2011. The congestive heart failure and the arrhythmia have not been re-evaluated, so outcome is unknown. Treatment is ongoing. MB decreased his Suboxone Film dose to 1 mg on 07-APR-2011 and since then has been feeling what he reports as "withdrawal". MB has been cutting the Film since he started using Film on an unknown date in 2010. MB reports that on MAY-2011 he increased his Suboxone film dose to 1 1/2 mg/daily and the withdrawal symptoms resolved on. He continues to take Coreg and Zestril as previously reported. On 01-JUL-2011 the Amiodarone was discontinued. Cutting the film is ongoing and MB has no plan to discontinue that practice; his physician is aware.

ISR#, Date Received, Age and Gender, Country	Type of Error	Cause	Outcome	Narrative
8136900-9, 2/14/12, 27 y.o./male (US)	Wrong technique	Knowledge deficit	Headaches	A 27-year-old male, with a history of opioid-type dependence, commenced 8 mg Suboxone Film, 12-16 mg daily on an unspecified date in Aug-2011. He used the Suboxone Film for induction and cut the Film to achieve his dose. His treatment with Suboxone continued. In Aug-2011, he began having headaches and these were still ongoing.

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/s/

CARLOS M MENA-GRILLASCA
03/26/2012

LUBNA A MERCHANT
03/26/2012

KELLIE A TAYLOR
03/26/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 9, 2012

To: Bob Rappaport, MD, Division Director
Division of Anesthesia, Analgesia, Addiction Products (DAAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Medical Policy Programs

Subject: DMPP Concurrence with submitted (Medication Guide)

Drug Name (established name): SUBOXONE (buprenorphine and naloxone)

Dosage Form and Route: sublingual film

Application Type/Number: NDA 22410

Supplement number: S-006
S-007

Applicant: Reckitt Benckiser Pharmaceuticals Inc.

1 INTRODUCTION

On September 30, 2011, Reckitt Benckiser Pharmaceuticals Inc., submitted for the Agency's review and approval supplements to Suboxone (buprenorphine and naloxone sublingual film) NDA 22410/S006 and NDA 22410/S007. The supplements include proposed changes to the dosage strengths in the Professional Information (PI).

The REMS is being reviewed by DRISK and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft Suboxone (buprenorphine and naloxone) sublingual film Medication Guide (MG) submitted on September 30, 2011.

3 REVIEW METHODS

- In our review of the MG, we have performed a side-by-side review of the Applicant's proposed MG against the currently approved Suboxone (buprenorphine and naloxone sublingual film) MG, dated August 30, 2010.

4 CONCLUSIONS

- The Applicant's proposed MG is acceptable as submitted.

5 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
03/12/2012

BARBARA A FULLER
03/12/2012

LASHAWN M GRIFFITHS
03/12/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-410/S006/S007

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Sullivan, Matthew

From: Mena-Grillasca, Carlos
Sent: Monday, May 21, 2012 12:46 PM
To: Sullivan, Matthew
Cc: Merchant, Lubna
Subject: RE: revised Suboxone labels/ N22410

Hi Matthew,

The Sponsor has revised the pouch label and carton labeling according to our recommendations. I do not have further comments at this time.

Thanks,
Carlos

Safety Evaluator | DMEPA | OMEPRM | OSE | CDER | FDA | 301.796.4073 | carlos.mena-grillasca@fda.hhs.gov

From: Sullivan, Matthew
Sent: Friday, May 18, 2012 5:07 PM
To: Mena-Grillasca, Carlos
Cc: Merchant, Lubna
Subject: RE: revised Suboxone labels/ N22410

I should have added your comments just so you didn't have to look them up.

- A. Pouch Labels (Proposed strengths: 4 mg/1 mg, 12 mg/3 mg)
 - a. Revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.
- B. Pouch Labels (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)
 - a. At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.
- C. Carton Labeling (Proposed strengths: 4 mg/1 mg, 12 mg/3 mg)
 - a. Revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.
- D. Carton Labeling (Currently marketed strengths: 1 mg/0.5 mg, 8 mg/2 mg)
 - a. At next printing revise the statement “Do not chew or swallow sublingual films” to read “Do not cut, chew or swallow sublingual film” and relocate to the Principal Display Panel to increase its prominence.

From: Sullivan, Matthew
Sent: Friday, May 18, 2012 4:18 PM
To: Mena-Grillasca, Carlos
Cc: Merchant, Lubna
Subject: revised Suboxone labels/ N22410

Carlos –

Your March review of the Suboxone film (b) (4) CMC supplements included some comments for the carton/container labeling. The Sponsor has emailed me a mock up of the change on a single carton and asked us to look at it before the revise them all.

Can you just see if this change meets your needs? If so, I'll have them revise them all.

original

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revised

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Thanks,
Matt

Matthew W. Sullivan, M.S.
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

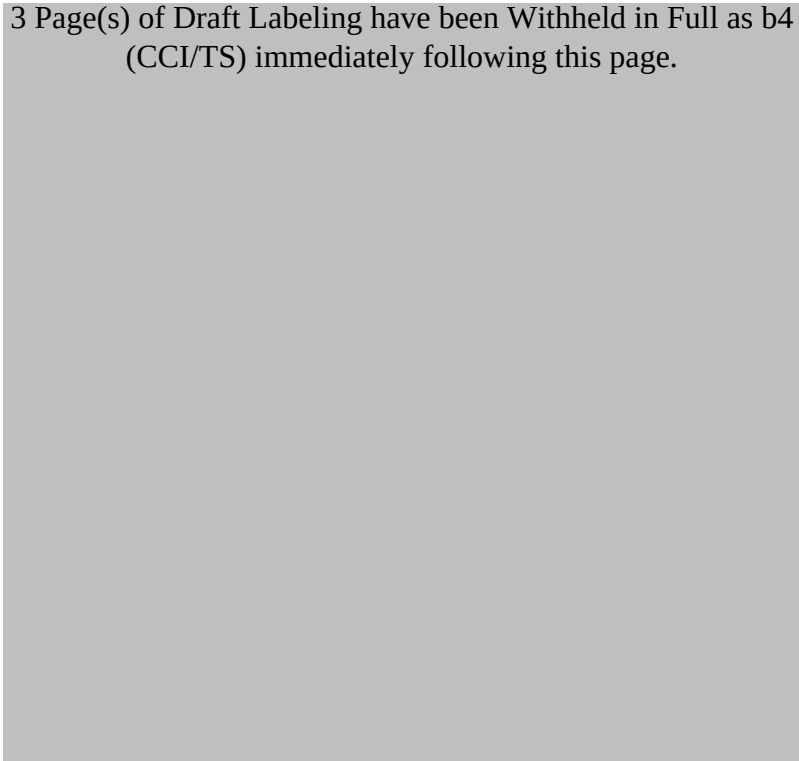
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/s/

MATTHEW W SULLIVAN
07/18/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE Attn: Mark Liberatore			FROM: Matt Sullivan, RPM, DAAAP	
DATE March 7, 2012	IND NO.	NDA NO. 22410	TYPE OF DOCUMENT CMC Supplements (S006 and S007)	DATE OF DOCUMENT September 29, 2011 (S006) September 30, 2011 (S006)
NAME OF DRUG Suboxone film		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 19, 2012
NAME OF FIRM: Reckitt Benckiser				
REASON FOR REQUEST				
I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):		☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES		☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL		☐ PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: S006 and S007 propose new strengths of Suboxone sublingual film (4mg/1mg and 12mg/3mg buprenorphine/naloxone, respectively). In addition to the consult request sent to OSE on February 8, 2012 (to review the revised REMS materials), new cartons are included in this submission. While they appear very similar to the approved cartons, we would like to request DMEPA input and concurrence on their acceptability. The cartons are attached, and are available electronically: NDA 022410/S006: \\cdsesub1\EVSPROD\NDA022410\0052\m1\us NDA 022410/S007: \\cdsesub1\EVSPROD\NDA022410\0053\m1\us Thanks				
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(CCI/TS) immediately following this page.



Back Front



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/s/

MATTHEW W SULLIVAN
03/07/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: OSE			FROM: Matt Sullivan, RPM, DAAAP	
DATE February 8, 2012	IND NO.	NDA NO. 22410	TYPE OF DOCUMENT CMC Supplements (S006 and S007)	DATE OF DOCUMENT January 26, 2012 (S006) January 27, 2012 (S007)
NAME OF DRUG Suboxone film		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE March 8, 2012
NAME OF FIRM: Reckitt Benckiser				
REASON FOR REQUEST I. GENERAL				
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE-NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH ☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):			STATISTICAL APPLICATION BRANCH ☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES			☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
☐ CLINICAL			☐ PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: S006 and S007 propose new strengths of Suboxone sublingual film (4mg/1mg and 12mg/3mg buprenorphine/naloxone, respectively). Changes to the REMS program and associated literature have also been proposed as a result. The Sponsor had originally proposed changes to the REMS which related to the new strength (b) (4). The Sponsor was informed that they needed to separate REMS changes into those that are germane to S006 or S007 (b) (4). The January 26, 2012, submission to S006, and January 27, 2012, submission to S007 represent these revised REMS documents. We request that DRISK review this REMS modification and comment as appropriate. NDA 022410/S006: \\cdsesub1\EVSPROD\NDA022410\0060\m1\us NDA 022410/S007: \\cdsesub1\EVSPROD\NDA022410\0061\m1\us Thanks				
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/s/

MATTHEW W SULLIVAN
02/08/2012

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Friday, January 06, 2012 4:01 PM
To: 'clorey.toombs@rb.com'
Subject: Re: NDA 22-410/S-006 and S-007

Dear Ms. Toombs,

We are reviewing your PAS submissions for 22-410 Suboxone (buprenorphine and nalaxone) film and request additional information as follows:

support the similarity of the proposed 4/1 strip with an approved strength of the same strip using f2 matrix with dissolution data generated with the approved dissolution method.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submissions by **January 13, 2012**. In addition, a copy of your response submitted by e-mail (swati.patwardhan@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Thank you

Swati Patwardhan
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment (ONDQA)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
01/06/2012



NDA 022410/S-007

**REVIEW EXTENSION –
CMC SUPPLEMENT**

Reckitt Benckiser Pharmaceuticals, Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Attention: Clorey Toombs
CMC Manager, Regulatory Affairs

Dear Ms. Toombs:

Please refer to your Supplemental New Drug Application (sNDA) submitted September 30, 2011, received September 30, 2011, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Suboxone (buprenorphine and naloxone) sublingual film.

On January 30, 2012, we received your January 27, 2012, major amendment to this application. The receipt date is within two months of the user fee goal date. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is March 30, 2012

If you have any questions, call Matt Sullivan, Senior Regulatory Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Sara Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

SARA E STRADLEY
01/30/2012



NDA 022410/S-007

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Reckitt Benckiser Pharmaceuticals, Inc.
10710 Midlothian Turnpike, Suite 430
Richmond, VA 23235

Attention: Clorey Toombs
CMC Manager, Regulatory Affairs

Dear Ms. Toombs:

We have received your September 30, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 022410
SUPPLEMENT NUMBER: 007
PRODUCT NAME: Suboxone (buprenorphine and naloxone) sublingual film
DATE OF SUBMISSION: September 30, 2011
DATE OF RECEIPT: September 30, 2011

This supplemental application proposes the following change: addition of a 12mg/3mg (buprenorphine/naloxone) strength.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 29, 2011, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be January 30, 2012.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Matthew W. Sullivan, MS
Senior Regulatory Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MATTHEW W SULLIVAN
01/18/2012

Stradley, Sara

From: Stradley, Sara
Sent: Friday, December 30, 2011 11:14 AM
To: 'clorey.Toombs@rb.com'
Cc: Sullivan, Matthew; Stradley, Sara
Subject: information request/NDA 022410 S-007

Hi Clorey

I am covering this application while Matt is on leave this week. We have the following information request and need this information no later than Thursday, Jan 5th.

Regarding Study RB-US-07-0001: Please provide the exposure data to the 12 mg/ 3mg formulation including:

1. subject identifier for all subjects with any exposure to the 12/3mg formulation,
2. total daily dose received for each subject,
3. how much of the total daily dose was dispensed as the 12mg/3mg formulation if the subject received a combination of dose strengths to reach the total daily dose (such as a total daily dose of 20 mg or 28 mg buprenorphine),
4. duration of the exposure to the 12/3 mg formulation for each subject

If a subject did not receive the 12/3mg formulation (for example, if a subject was taking a total daily dose of 12/3mg but staff dispensed 2/0.5 mg films and the subject took 6 films per day) do not include this data. While it says that this type of dispensing was not recommended in the study report, it appears that some subjects may have had their medication dispensed this way based on the disp dataset.

Separate subjects who were instructed to take the 12/3 mg formulation sublingually from those who were instructed to take it buccally, in reporting the exposure data.

Thanks

Sara E. Stradley, MS
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research
phone # 301-796-1298
fax # 301-796-9713
email: sara.stradley@fda.hhs.gov

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/s/

SARA E STRADLEY
12/30/2011