AUSTRALIAN PRODUCT INFORMATION

SUBOXONE® FILM (BUPRENORPHINE/NALOXONE)

WARNINGS

Hazardous and harmful use

Although SUBOXONE FILM is indicated for the treatment of opioid dependence it still poses risks of hazardous and harmful use which can lead to overdose and death. Monitor the patient's ongoing risk of hazardous and harmful use regularly during opioid substitution therapy with SUBOXONE FILM (see section 4.4. Special Warnings and Precautions for Use).

Life threatening respiratory depression

Serious, life-threatening or fatal respiratory depression may occur with the use of SUBOXONE FILM. Be aware of situations which increase the risk of respiratory depression, and monitor patients closely, especially on initiation or following a dose increase (see section 4.4 Special Warnings and Precautions for Use).

Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol

Concomitant use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Patients and their caregivers should be made aware of the symptoms of respiratory depression. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking SUBOXONE FILM.

1 NAME OF THE MEDICINE

SUBOXONE FILM contains buprenorphine (as hydrochloride) and naloxone (as hydrochloride dihydrate) at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SUBOXONE FILM is available in four dosage strengths:

2 mg buprenorphine (as hydrochloride) + 0.5 mg naloxone (as hydrochloride dihydrate)
4 mg buprenorphine (as hydrochloride) + 1 mg naloxone (as hydrochloride dihydrate)
8 mg buprenorphine (as hydrochloride) + 2 mg naloxone (as hydrochloride dihydrate) and
12 mg buprenorphine (as hydrochloride) + 3 mg naloxone (as hydrochloride dihydrate).

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg /mL at 37°C, pH 4.1). Chemically, it is 21- Cyclopropyl-7α-[(S) -1- hydroxy-1, 2, 2 -trimethylpropyl]-6, 14-endo-ethano-6, 7, 8, 14-tetrahydrooripavine hydrochloride. Buprenorphine hydrochloride has the molecular formula C_{29} H_{41} NO_4 HCl and the molecular weight is 504.09. The CAS number is 53152-21-9.

Naloxone hydrochloride is a white to slightly off-white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali. Chemically, it is (-)-17-Allyl-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. Naloxone hydrochloride has the molecular formula C_{19} H_{21} NO_4 HCl .$2H_2O$ and the molecular weight is 399.87.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SUBOXONE FILM is a soluble film intended for sublingual and or buccal administration only.
SUBOXONE FILM is supplied as an orange rectangular soluble film with a white printed logo in four dosage strengths:

- "N2" for 2/0.5 mg buprenorphine/naloxone
- "N4" for 4/1 mg buprenorphine/naloxone*
- "N8" for 8/2 mg buprenorphine/naloxone and
- "N12" for 12/3 mg buprenorphine/naloxone*.

* Not supplied

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of opioid dependence within a framework of medical, social and psychological treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with SUBOXONE FILM is intended for adults and children aged 16 years or over who have agreed to be treated for opioid dependence.

SUBOXONE FILM and SUBOXONE TABLET do not meet all criteria for bioequivalence (see section 5.2 Pharmacokinetic Properties). Patients being switched between tablets and soluble films may therefore require dosage adjustment.

The routes of administration of SUBOXONE FILM is sublingual and buccal only. The film formulation is not designed to be split or broken.

SUBOXONE FILMS should not be swallowed whole as this reduces the bioavailability of the medicine. Physicians must advise patients that the sublingual and buccal route are the only effective and safe route of administration for this medicine.

Please note: The following instructions refer to the buprenorphine content of each dose.

Method of Administration

Sublingual Administration

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

Buccal Administration

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

No food or drink should be consumed until the film is completely dissolved. SUBOXONE FILM should NOT be chewed, swallowed, or moved from placement.

Starting SUBOXONE FILM

An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms due to inadequate dosage.

Prior to induction, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use and the degree or level of opioid dependence.

Due to naloxone exposure being somewhat higher following buccal administration than sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimise naloxone exposure and to reduce the risk of precipitated withdrawal.

Induction onto SUBUTEX (buprenorphine tablets) is recommended when there is doubt about the level of dependence or previous opioid use, to avoid precipitating opioid withdrawal. Patients can be switched to SUBOXONE FILM on the third day.

When initiating buprenorphine treatment, the physician should be aware of the partial agonist profile of the molecule to the μ opioid receptors, which can precipitate withdrawal in opioid-dependent patients if given too soon after the administration of heroin, methadone or another opioid. To avoid precipitating withdrawal, induction with buprenorphine should be undertaken when objective and clear signs of withdrawal are evident.

Patients taking Heroin (or Other Short-acting Opioids)

When treatment starts the dose of SUBOXONE FILM should be taken at least 6 hours after the patient last used opioids and when the objective signs of withdrawal appear. The Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment however clinical assessment of withdrawal symptoms with consideration of the patient's baseline presentation is important, particularly for patients in mild withdrawal (COWS score of 5-12). The recommended starting dose is 4-8 mg SUBOXONE FILM on Day One, with a possible additional 4 mg depending on the individual patient's requirement. The suggested target total dose for Day One is in the range of 8-12 mg SUBOXONE FILM. For patients with moderate or severe withdrawal at the time of the first dose, an initial dose of 8 mg may be appropriate with an additional 4 mg depending on the individual patient's requirement to a total maximum of 12 mg on Day 1.

Lower doses (e.g. 2 or 4 mg total on Day 1) are suited to those with low or uncertain levels of opioid dependence, with high risk polydrug use (alcohol, benzodiazepines) or with other severe medical complications. Seek specialist advice if concerned.

Patients on Methadone

Before starting treatment with SUBOXONE FILM, the maintenance dose of methadone should be reduced to the minimum methadone daily dose that the patient can tolerate. The first dose of SUBOXONE FILM should be taken at least 24 hours after the patient last used methadone. An initial dose of 2 mg SUBOXONE FILM may be administered when moderate withdrawal is apparent (COWS ≥ 13). An additional dose of 6 mg SUBOXONE FILM can be administered one hour later if the initial dose does not precipitate withdrawal. Supplementary doses can be administered every 1 to 3 hours according to withdrawal severity:

- 0 mg if there is no or minimal withdrawal (COWS < 5);
- 4 mg if there is mild withdrawal (COWS 5-12);
- 8 mg if there is moderate to severe withdrawal (COWS ≥ 13).

The suggested target total dose for Day One is in the range of 8 – 16 mg SUBOXONE FILM. A maximum daily dose of 32 mg should not be exceeded.

During the initiation of treatment, patients need frequent monitoring. SUBOXONE FILM should be dispensed in multiple doses over the first 4 to 6 hours of the transfer. Dosing supervision is recommended to ensure proper placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Switching between treatments for opioid dependence

Patients should be closely monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported.

Switching between SUBOXONE FILM strengths

The sizes and the compositions of the four units of SUBOXONE FILMs, i.e. 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE 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.

Switching between sublingual and buccal sites of administration

The systemic exposure of buprenorphine between buccal and sublingual administration of SUBOXONE FILM is similar. Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

Dose adjustment in hepatic impairment

Use of SUBOXONE FILM is contraindicated in patients with severe hepatic impairment.

SUBOXONE FILM may not be appropriate for patients with moderate hepatic impairment. SUBOXONE FILM may be used with caution for maintenance treatment in patients with moderate hepatic impairment, who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment prescribed SUBOXONE should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower initial doses and cautious titration of dosage may be required in patients with moderate hepatic impairment.

No dosage adjustment is needed in patients with mild hepatic impairment.

Dosage Adjustment and Maintenance

The dose of SUBOXONE FILM should be adjusted progressively according to the clinical effect in the individual patient. The dosage is adjusted in increments or decrements of 2 – 8 mg buprenorphine to a level that maintains the patient in treatment and suppresses opioid withdrawal effects according to reassessments of the clinical and psychological status of the patient.

Most patients require daily buprenorphine doses in the range 12-24 mg to achieve stabilisation, although some patients require higher (e.g. up to 32 mg/day) or lower (4-8 mg/day) doses to achieve their treatment goals. During maintenance therapy, it may be necessary to periodically restabilise patients to new maintenance doses in response to changing patient needs.

Less than daily dosing

After a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

In some patients, after a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32 mg.

The patient should be observed following the first multi-dose administration to initiate the less-than-daily dosing regimen and whenever treated with high doses. Patients who sporadically use concomitant CNS-active medications or substances should be monitored closely.

Reducing Dosage and Stopping Treatment

The decision to discontinue therapy with SUBOXONE FILM should be made as part of a comprehensive treatment plan. A possible gradual dose taper over a period of 21 days is shown in Table 1.

Table 1.	Gradual dose taper schedule		
Week	**20 mg Maintenance dose**	**16 mg Maintenance dose**	**8 mg Maintenance dose**
1	16 mg	12 mg	8 mg
2	8 mg	8 mg	4 mg
3	4 mg	4 mg	4 mg

4.3 CONTRAINDICATIONS

Hypersensitivity to buprenorphine or naloxone or any other component of the soluble film.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency (Child-Pugh C).
Acute intoxication with alcohol or other CNS depressant.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

SUBOXONE FILM should be administered with caution in debilitated patients and those with impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (e.g. Addison's disease); CNS depression or coma; toxic psychoses; acute alcoholism; or delirium tremens.

Buprenorphine increases intracholedochal pressure as do other opioids. Therefore, caution should be exercised when SUBOXONE FILM is to be administered to patients with dysfunction of the biliary tract.

As with other opioids, caution is advised in patients using buprenorphine and having hypotension, prostatic hypertrophy or urethral stenosis.

Opioids may produce orthostatic hypotension in ambulatory patients.

As with other mu-opioid receptor agonists, the administration of SUBOXONE FILM may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Use in the elderly

The safety and efficacy of buprenorphine in elderly patients over 65 years have not been established.

Misuse, abuse and diversion

Although SUBOXONE FILM is indicated for the treatment of opioid dependence it still poses risks of hazardous and harmful use which can lead to overdose and death. Monitor the patient's ongoing risk of hazardous and harmful use regularly during opioid substitution therapy with SUBOXONE FILM.

SUBOXONE can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. SUBOXONE misuse by someone other than the intended patient poses the additional risk of new opioid dependent individuals using buprenorphine as the primary opioid of abuse and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft, including in the home. Sub-optimal treatment with SUBOXONE may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBOXONE may continue

responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. To minimise risk of misuse, abuse or diversion, appropriate precautions should be taken when prescribing and dispensing SUBOXONE, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Patients dependent upon concomitant CNS-active substances, including alcohol, should not be treated with the increased doses required by the less-than-daily dosing regimen intended for use in a supervised dose setting. Patients with sporadic use of concomitant non-opioid medications should be monitored closely and all patients dosed on a less-than-daily basis should be observed following the first multi-dose administration when initiating less-than-daily dosing or whenever treated with high doses.

Respiratory Depression

Serious, life-threatening or fatal respiratory depression may occur with the use of SUBOXONE FILM. Be aware of situations which increase the risk of respiratory depression and monitor patients closely, especially on initiation or following a dose increase.

SUBOXONE FILM is intended for sublingual or buccal use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when buprenorphine was used in combination with benzodiazepines, in opioid naïve individuals, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBOXONE FILM.

In the event of depression of respiratory or cardiac function, see section 4.9 Overdose.

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

SUBOXONE FILM may cause severe, possible fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

CNS Depression

Concomitant use of opioids with benzodiazepines, tranquillisers, sedatives, hypnotics, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see section 4.5 Interactions with other medicines and other forms of interactions). Patients and their caregivers should be made aware of the symptoms of respiratory depression. Patients and their caregivers should also be informed of the potential harms of consuming alcohol while taking SUBOXONE FILM.

SUBOXONE FILM should be used cautiously with MAOIs, based on experience with morphine.

Hepatitis, Hepatic Events

Cases of acute hepatic injury have been reported in opioid-dependent patients, both in clinical trials and post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose-related and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, liver enzyme abnormalities, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral

nucleoside analogues, or drug misuse by injection) could promote the occurrence of such hepatic injuries. These co-factors must be taken into account before prescribing SUBOXONE FILM and during treatment monitoring. Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicines (see section 4.5 Interactions) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicine may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to opioid dependence. If treatment is continued, hepatic function should be monitored closely.

Use in hepatic Impairment

Buprenorphine and naloxone are extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study, in which a SUBOXONE 2.0/0.5 mg (buprenorphine/naloxone) sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Plasma levels were found to be elevated for buprenorphine and naloxone in patients with moderate to severe hepatic impairment (Table 2). Patients with severe hepatic impairment experienced substantially greater increases in exposure to naloxone relative to buprenorphine and patients with moderate hepatic impairment experienced greater increases in exposure to naloxone relative to buprenorphine. The clinical impact in terms of efficacy/safety is unknown, but is likely to be greater for those with severe hepatic impairment than those with moderate hepatic impairment.

The doses of buprenorphine and naloxone in SUBOXONE cannot be individually titrated. As such, SUBOXONE should be avoided in patients with severe hepatic impairment. Use of SUBOXONE may not be appropriate in those with moderate hepatic impairment. It may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine-only product. Patients with moderate hepatic impairment should be monitored for signs and symptoms of precipitated opioid withdrawal. In addition, lower initial doses and cautious titration of dosage may be required in patients with moderate hepatic impairment. As with all patients treated with SUBOXONE, liver function tests should be monitored prior to and during treatment. See also section 4.2 Dose and Method of administration.

Table 2: Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following buprenorphine/naloxone administration (change relative to healthy subjects)

PK parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
BUPRENORPHINE			
C_{max}	1.2 fold increase	1.1 fold increase	1.7 fold increase
AUC_{last}	Similar to control	1.6 fold increase	2.8 fold increase
NALOXONE			
C_{max}	Similar to control	2.7 fold increase	11.3 fold increase
AUC_{last}	0.2 fold decrease	3.2 fold increase	14 fold increase

In the same study, changes in C_{max} and AUC_{last} of buprenorphine and naloxone in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

Use in renal impairment

Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine. Therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} <30 mL/min), which may require dose adjustment.

Head Injury and Increased Intracranial Pressure

SUBOXONE FILM, like other potent opioids may itself elevate cerebrospinal fluid pressure, which may cause seizures, and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased, or history of seizure. SUBOXONE FILM can produce miosis and changes in the level of consciousness, or changes in the perception of pain as a symptom of disease and may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

Opioid Withdrawal Effects

Because SUBOXONE FILM contains naloxone, it is highly likely to produce marked and intense opioid withdrawal symptoms if injected by patients treated with SUBUTEX or SUBOXONE or by persons dependent on full opioid agonists such as heroin, oxycodone, morphine or methadone.

SUBOXONE FILM may produce withdrawal symptoms in opioid dependent subjects if it is administered too soon after another opioid. Buprenorphine is a partial agonist at the μ (mu)-opioid receptor and studies in animals, as well as clinical experience, have shown that buprenorphine may produce dependence, but at a lower level than morphine. Consequently, it is important to follow the recommendations in section 4.2 Dose and Method of administration. Withdrawal symptoms may also be associated with suboptimal dosing. Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

Neonatal Abstinence Syndrome

Chronic use of buprenorphine by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, apnoea, convulsions or bradycardia) in the neonate. In many reported cases the withdrawal was serious and required treatment. The syndrome is generally delayed for several hours to several days after birth (see section 4.6 Use in Pregnancy). Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Allergic Reactions

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

Paediatric Use

SUBOXONE FILM is not recommended for use in children. The safety and effectiveness of SUBOXONE FILM in subjects below the age of 16 has not been established. Due to limited amount of available data, patients between 16 and 18 years of age should be closely monitored during treatment.

Effects on Laboratory Tests

Athletes should be aware that this medicine may cause a positive reaction to “anti-doping” tests.

Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received doses as low as 2 mg of buprenorphine sublingual tablet for analgesia. SUBOXONE is not appropriate as an analgesic.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Alcohol

Alcohol increases the sedative effect of buprenorphine/naloxone. SUBOXONE should not be used together with alcoholic drinks and must be used cautiously with medicines containing alcohol (see section 4.4 Special Warnings and Precautions for Use).

Benzodiazepines

This combination may result in death due to respiratory depression of central origin; therefore, patients must be closely monitored when prescribed this combination and this combination should be avoided where there is a risk of misuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see section 4.4 Special Warnings and Precautions for Use).

Other central nervous system depressants

Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machinery dangerous. Examples include opioids (e.g. methadone, analgesics, and antitussives), gabapentinoids, cannabis, certain antidepressants, antihistamines (e.g. sedating H1-receptor antagonists), barbiturates, anxiolytics, neuroleptics, clonidine (see section 4.4 Special Warnings and Precautions for Use).

Opioid analgesics

The analgesic properties of other opioids such as methadone and level III analgesics may be reduced in patients receiving treatment with buprenorphine/naloxone for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving SUBOXONE. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining. Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see section 4.4 Special Warnings and Precautions for Use).

Naltrexone and other opioid antagonists

Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of SUBOXONE FILM. Patients maintained on SUBOXONE FILM may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.

CYP3A4 inhibitors

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBOXONE FILM should be closely monitored and may require dose reduction if combined with potent CYP3A4 inhibitors e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, azole antifungals like ketoconazole or itraconazole, calcium channel antagonists, and macrolide antibiotics.

CYP3A4 inducers

Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in under-treatment of opioid dependence with buprenorphine; therefore, it is recommended that patients receiving SUBOXONE FILM should be

closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, and rifampicin) are co-administered.

Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue buprenorphine if serotonin syndrome is suspected. Examples of serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, serotonin precursors (e.g., tryptophan), drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol, lithium, St. John's wort), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2). Dietary administration of SUBOXONE TABLETS to rats at doses of 47 mg/kg/day or greater (estimated respective buprenorphine and naloxone exposures 14 and 24 times the anticipated clinical exposure, based on plasma AUC) resulted in reduced female conception rates. A dietary dose of 9.4 mg/kg/day (twice the anticipated clinical exposure for both buprenorphine (based on AUC) and naloxone (based on mg/m^2) had no adverse effect on fertility.

Use in Pregnancy – Pregnancy Category C

In rats, oral administration of buprenorphine at doses up to 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2) prior to and during gestation and lactation resulted in reduced implantation, fewer live births, and reduced pup weight gain and survival. There was no evidence of teratogenicity in rats and rabbits following parenteral administration of buprenorphine during the period of organogenesis, although there was embryofoetal toxicity, and reduced pup viability and developmental delays in rats. There was no evidence of teratogenicity in rats and rabbits following oral or intramuscular administration of maternally toxic doses of combinations of buprenorphine + naloxone during the period of organogenesis, although post-implantation losses were increased. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response).

Buprenorphine readily crosses the placental barrier and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. SUBOXONE FILM should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

Data on the use of buprenorphine in pregnancy, and its impact on the mother and foetus, are limited. Data from randomised, controlled trials and observational studies do not indicate an increased risk of maternal or foetal adverse outcomes compared to methadone.

Use in Lactation

Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration

of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response). The no effect level for developmental effects was twice the maximum clinical dose, based on mg/m^2. In two studies of thirteen women, buprenorphine was found in low levels in human breast milk. In both studies the estimated infant dose was <1% of the maternal dose. Because buprenorphine is excreted into human milk, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBOXONE FILM and any potential adverse effects on the breastfed child from the treatment or the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

SUBOXONE may influence the ability to drive and use machinery when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions). Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that SUBOXONE therapy does not adversely affect their ability to engage in such activities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Safety Study of SUBOXONE FILM

The clinical safety of SUBOXONE FILM was evaluated in a trial (RB-US-07-0001) of 382 patients stabilised on SUBOXONE TABLETS for at least 30 days and then switched to SUBOXONE FILM for maintenance treatment. Two hundred and forty-nine (249) patients completed at least 12 weeks of dosing with the SUBOXONE FILM. Patients received SUBOXONE FILM sublingually or buccally in a 1:1 ratio (N=194 sublingually, N=188 buccally). Adjunctive treatment was "treatment as usual" with varying levels of counselling and behavioural treatment. Treatment was conducted on an outpatient basis. Among all patients who received SUBOXONE FILM either sublingually or buccally, the most common treatment emergent adverse events were oral mucosal erythema, sinusitis, nausea, toothache, pain and upper respiratory tract infection. The most common treatment emergent adverse event for the patients administered SUBOXONE FILM sublingually was upper respiratory tract infection (4 patients, 2.1%) and for patients administered SUBOXONE FILM buccally were oral mucosal erythema (6 patients, 3.2%), nausea (4 patients, 2.1%) and sinusitis (4 patients, 2.1%). All other adverse events were reported in 3 (1.5% or 1.6%, respectively) or fewer patients.

Adverse events reported to occur to at least 1% of patients being treated with SUBOXONE FILM in this trial are shown in Table 3.

Table 3 Adverse Events (≥1%) by Body System and Treatment Group in Study RB-US-07-0001, Sublingual and Buccal Administration

System Organ Class Preferred term	**Sublingual N=194**	**Buccal N=188**
Infections and Infestations		
Sinusitis	3 (1.5%)	4 (2.1%)
Upper respiratory tract infection	4 (2.1%)	2 (1.1%)
Pharyngitis streptococcal	2 (1.0%)	2 (1.1%)
Urinary tract infection	3 (1.5%)	1 (0.5%)

System Organ Class Preferred term	**Sublingual N=194**	**Buccal N=188**
Influenza	2 (1.0%)	1 (0.5%)
Tooth abscess	2 (1.0%)	0 (0%)
Nasopharyngitis	0 (0%)	3 (1.6%)
Cellulitis	0 (0%)	2 (1.1%)
Gastrointestinal Disorders		
Glossodynia	3 (1.5%)	1 (0.5%)
Hypoaesthesia oral	2 (1.0%)	1 (0.5%)
Nausea	3 (1.5%)	3 (1.6%)
Oral mucosal erythema	2 (1.0%)	6 (3.2%)
Toothache	2 (1.0%)	4 (2.1%)
Vomiting	3 (1.5%)	2 (1.1%)
Gastrooesophageal reflux disease	1 (0.5%)	3 (1.6%)
Constipation	1 (0.5%)	2 (1.1%)
Musculoskeletal and Connective Tissues Disorders		
Back pain	3 (1.5%)	1 (0.5%)
Arthralgia	2 (1.0%)	0 (0%)
Musculoskeletal pain	2 (1.0%)	0 (0%)
Muscle spasms	0 (0%)	2 (1.1%)
Psychiatric Disorders+		
Stress	2 (1.0%)	1 (0.5%)
Drug dependence (craving)	0 (0%)	2 (1.1%)
Injury, Poisoning and Procedural Complications		
Skin laceration	2 (1.0%)	1 (0.5%)
Road traffic accident	0 (0%)	2 (1.1%)
General Disorders and Administration Site Conditions		
Pain	3 (1.5%)	3 (1.6%)
Oedema peripheral	1 (0.5%)	2 (1.1%)
Nervous System Disorders		
Headache	2 (1.0%)	3 (1.6%)
Migraine	1 (0.5%)	2 (1.1%)
Renal and Urinary Disorders		
Nephrolithiasis	2 (1.0%)	2 (1.1%)
Metabolism and Nutrition Disorders		
Gout	1 (0.5%)	2 (1.1%)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	0 (0%)	2 (1.1%)

System Organ Class Preferred term	Sublingual N=194	Buccal N=188
Skin and Subcutaneous Tissue Disorders		
Dermatitis contact	2 (1.0%)	0 (0%)
Pregnancy, Puerperium and Perinatal Conditions		
Pregnancy	2 (1.0%)	0 (0%)

* AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 terminology.

Clinical trials of SUBOXONE TABLETS

Adverse events reported to occur to at least 1% of patients being treated in clinical trials of SUBOXONE TABLETS (CR96/013 + CR96/014) are shown in Tables 4 and 5.

Table 4. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/013

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) TABLETS 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) TABLETS 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Body as a Whole				
Abscess	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)	19 (6.0%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)	24 (7.6%)
Fever	3 (2.8%)	3 (2.9%)	4 (3.7%)	10 (3.2%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)	93 (29.3%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)	25 (7.9%)
Accidental Injury	2 (1.9%)	5 (4.9%)	5 (4.7%)	12 (3.8%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)	63 (19.9%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)	31 (9.8%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)	24 (7.6%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)	86 (27.1%)
Cardiovascular System				
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)	21 (6.6%)
Digestive System				
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)	24 (7.6%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)	25 (7.9%)
Dyspepsia	4 (3.7%)	5 (4.9%)	5 (4.7%)	14 (4.4%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)	42 (13.2%)

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) TABLETS 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) TABLETS 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)	21 (6.6%)
Metabolic/Nutritional Disorders				
Peripheral Edema	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)
Musculoskeletal System				
Myalgia	4 (3.7%)	1 (1.0%)	1 (0.9%)	6 (1.9%)
Nervous System				
Agitation	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Anxiety	3 (2.8%)	5 (4.9%)	4 (3.7%)	12 (3.8%)
Dizziness	5 (4.7%)	3 (2.9%)	4 (3.7%)	12 (3.8%)
Hyperkinesia	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Hypertonia	2 (1.9%)	0	2 (1.9%)	4 (1.3%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)	54 (17.0%)
Nervousness	5 (4.7%)	6 (5.8%)	4 (3.7%)	15 (4.7%)
Paresthesia	3 (2.8%)	3 (2.9%)	0	6 (1.9%)
Somnolence	8 (7.5%)	4 (3.9%)	2 (1.9%)	14 (4.4%)
Thinking Abnormal	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Tremor	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Respiratory System				
Cough Increased	1 (0.9%)	2 (1.9%)	2 (1.9%)	5 (1.6%)
Pharyngitis	2 (1.9%)	4 (3.9%)	1 (0.9%)	7 (2.2%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)	29 (9.1%)
Skin And Appendages				
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)	39 (12.3%)
Special Senses				
Amblyopia	3 (2.8%)	1 (1.0%)	0	4 (1.3%)
Lacrimation Disorder	0	4 (3.9%)	6 (5.6%)	10 (3.2%)
Urogenital System				
Dysmenorrhea	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Urinary Tract Infection	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)

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

Table 5. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/014

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Body as a Whole	
Abscess	17 (3.6%)
Allergic Reaction	8 (1.7%)
Asthenia	48 (10.2%)
Chills	44 (9.3%)
Cyst	7 (1.5%)
Edema, Face	8 (1.7%)
Fever	36 (7.6%)
Flu Syndrome	89 (18.9%)
Headache	202 (42.8%)
Infection	5 (1.1%)
Infection, Viral	5 (1.1%)
Accidental Injury	72 (15.3%)
Malaise	9 (1.9%)
Neck Rigid	5 (1.1%)
Pain	197 (41.7%)
Pain, Abdomen	77 (16.3%)
Pain, Back	132 (28.0%)
Pain, Chest	23 (4.9%)
Pain, Neck	12 (2.5%)
Withdrawal Syndrome	194 (41.1%)
Cardiovascular System	
Hypertension	17 (3.6%)
Migraine	13 (2.8%)
Vasodilation	29 (6.1%)
Digestive System	
Abscess, Periodontal	10 (2.1%)
Anorexia	16 (3.4%)
Constipation	115 (24.4%)
Diarrhea	50 (10.6%)
Dyspepsia	45 (9.5%)
Flatulence	11 (2.3%)
Gastrointestinal Disorder	
Liver Function Abnormal	18 (3.8%)
Nausea	76 (16.1%)
Stomatitis	5 (1.1%)
Tooth Disorder	37 (7.8%)
Ulcer, Mouth	6 (1.3%)
Vomiting	61 (12.9%)
Hemic/Lymphatic System	
Anemia	7 (1.5%)
Ecchymosis	6 (1.3%)
Lymphadenopathy	5 (1.1%)
Metabolic/Nutritional Disorders	
Peripheral Edema	24 (5.1%)
Hyperglycemia	5 (1.1%)
Weight Decreased	15 (3.2%)
Musculoskeletal System	
Arthralgia	20 (4.2%)
Arthritis	5 (1.1%)
Leg Cramps	13 (2.8%)
Joint Disorder	9 (1.9%)
Myalgia	31 (6.6%)
Nervous System	
Agitation	10 (2.1%)
Anxiety	65 (13.8%)
Depression	70 (14.8%)
Dizziness	33 (7.0%)
Dream Abnormalities	9 (1.9%)
Drug Dependence	9 (1.9%)
Hypertonia	9 (1.9%)
Insomnia	138 (29.2%)
Libido Decreased	9 (1.9%)
Nervousness	42 (8.9%)
Paresthesia	28 (5.9%)
Somnolence	40 (8.5%)
Thinking Abnormal	6 (1.3%)
Tremor	7 (1.5%)
Respiratory System	
Asthma	21 (4.4%)
Bronchitis	9 (1.9%)
Cough Increased	36 (7.6%)
Dyspnea	9 (1.9%)
Lung Disorder	10 (2.1%)
Pharyngitis	64 (13.6%)
Pneumonia	12 (2.5%)
Respiratory Disorder	7 (1.5%)
Rhinitis	75 (15.9%)
Sinusitis	7 (1.5%)
Sputum Increased	5 (1.1%)
Yawn	6 (1.3%)
Skin and Appendages	
Acne	5 (1.1%)
Dermatological Contact	5 (1.1%)
Herpes Simplex	6 (1.3%)
Nodule, Skin	6 (1.3%)
Pruritus	11 (2.3%)

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)	Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE TABLET Subjects N=472 n (%)
Skin Dry	6 (1.3%)	**Urogenital System**	
Sweat	74 (15.7%)	Dysmenorrhea	19 (4.0%)
Urticaria	6 (1.3%)	Dysuria	9 (1.9%)
Special Senses		Hematuria	8 (1.7%)
Amblyopia	5 (1.1%)	Impotence	11 (2.3%)
Conjunctivitis	14 (3.0%)	Urinary Tract Infection	19 (4.0%)
Eye Disorder	8 (1.7%)	Urine Abnormality	12 (2.5%)
Lacrimation Disorder	14 (3.0%)	Vaginitis	11 (2.3%)
Pain, Ear	8 (1.7%)		

The most common (≥10%) adverse events reported were those related to withdrawal symptoms (e.g. insomnia, headache, constipation, nausea, abdominal pain, diarrhoea, muscle aches, anxiety, sweating). In patients with marked opioid dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Note - Patients enrolled in study RB-US-07-0001 on the soluble film were on a stable buprenorphine treatment prior to study initiation, while patients enrolled in studies CR96/013 and CR96/014 were buprenorphine-naïve individuals. As a result, the number of AEs observed in study RB-US-07-0001 is likely to be lower than that observed in studies CR96/013 and CR96/014.

Post-marketing experience with buprenorphine alone

Post-marketing experience with buprenorphine alone has been associated with the following side effects: respiratory depression (see section 4.4 Special Warnings and Precautions for Use) and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, foetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, urinary retention, vertigo, drug dependence, headache, nausea, vomiting, drug withdrawal syndrome, peripheral oedema, heart rate and rhythm disorders, and deaths.

Cases of hepatitis, jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and elevations in hepatic transaminases have been reported with buprenorphine use (see section 4.4 Special Warnings and Precautions for Use).

In cases of intravenous misuse of buprenorphine, local reactions, sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections have been reported.

Cases of acute or chronic hypersensitivity have been reported with buprenorphine with symptoms including rashes, hives, pruritus and reported cases of bronchospasm, angioneurotic oedema, and anaphylactic shock (see section 4.4 Special Warnings and Precautions for Use and section 4.3 Contraindications).

Very rare (<0.01%) side effects: loss of consciousness, cognitive disorders, psychosis, hallucinations, suicidal ideation, disorders of pregnancy (such as miscarriage and termination of pregnancy, premature birth, placental abruption, prolonged labour), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, decreased oxygen saturation, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, cleft palate, Klinefelter's Syndrome, intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, infant respiratory distress syndrome and subarachnoid bleeding), heart murmur, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, pulmonary oedema, septic shock, infections (including sepsis, septic arthritis and septic embolus, staphylococcal sacroileitis, brain abscess, pneumonia and endocarditis and amniotic fluid infection) events associated with intravenous

misuse (such as cutaneous ulceration, eschar, lividoid and necrotic lesions and penile and scrotal lesion), aphasia, aphonia, slurred speech, diplopia, facial palsy, ascites and lympodoema, pulmonary oedema, pulmonary artery thrombosis, pericardial effusion, shock, cerebrovascular accident, Popeye syndrome, intracranial haemorrhage, nephropathy, colic, denutrition splenic infarction, electrolyte imbalance (such as hyperkalaemia, hyponatraemia and hypoglycaemia), deaths (including death from suicide and sudden infant death syndrome) and unusual reactions. The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style, environmental factors, and concomitant illicit and licit opioid use of the population under treatment.

Post-marketing experience with SUBOXONE TABLETS

A post-marketing study looking at injecting practices in Australia suggested that the combination of buprenorphine and naloxone is less commonly injected than buprenorphine alone.

Additionally, post-marketing experience with SUBOXONE TABLETS for treatment of opioid dependence has been associated with the following side effects: anxiety, hyperhidrosis, syncope, insomnia, reduced feeling, anorexia (see also Tables 4 and 5 above), amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath, and suicide ideation. Treatment with SUBOXONE has been associated with orthostatic hypotension.

Additionally, post-marketing experience with SUBOXONE TABLETS for treatment of opioid dependence has been associated very rarely (<0.01%) with the following side effects: attempted suicide, disorders of pregnancy (such as premature birth), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, macrocephaly, meconium staining and aspiration, decreased oxygen saturation, neonatal aspiration, asphyxia, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, low birth weight, Klinefelter's Syndrome, mitochondrial disease, abnormal behaviour, developmental delay, developmental speech disorder intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, subarachnoid bleeding and sudden infant death syndrome), pancreatitis, loss of consciousness, depression of consciousness, coordination disturbance, hallucinations, psychosis, mental disturbance and altered mental state, cerebral oedema, heart rate and rhythm disorders, septic shock, infections (including sepsis, pneumonia, chorioamniotitis and amniotic fluid infection) events associated with intravenous misuse (such as cellulitis), blurred vision, papilloedema, ascites and peripheral oedema, renal failure, adrenal insufficiency, electrolyte imbalance (such as hyperkalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia and hypoglycaemia) and deaths (including death from suicide and sudden infant death syndrome). The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style, environmental factors, and concomitant illicit and licit opioid use of the population under treatment.

Post-marketing experience with SUBOXONE FILM

Post-marketing experience with SUBOXONE FILM for the treatment of opioid dependence has been most frequently associated with the following; adverse reactions appearing in at least 1% of reports by healthcare professionals are included in Table 6.

Table 6: Spontaneous adverse drug reactions collected through post-marketing surveillance reported by body system	
System Organ Class	**Preferred term**
Nervous system disorders	Headache
Gastrointestinal disorders	Glossitis Nausea Stomatitis Tongue disorder Vomiting
Skin and subcutaneous disorders	Rash
General disorders and administration site conditions	Drug ineffective Drug withdrawal syndrome Oedema peripheral

4.9 OVERDOSE

Manifestations of acute overdose include miosis, sedation, hypotension, respiratory depression and death. Nausea and vomiting may be observed.

The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment

In the event of depression of respiratory or cardiac function, 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 following standard intensive care measures. The patient should be transferred to an environment within which full resuscitation facilities are available.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of SUBOXONE FILM should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms, so a continuing infusion may be necessary. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the opioid dependent patient for illicit opioid medicines.

During clinical pharmacology studies in opioid dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.

Naloxone is an antagonist at μ (mu), δ (delta), and κ (kappa) opioid receptors. Because of its almost complete first pass metabolism, naloxone administered orally, sublingually or buccally has no detectable pharmacological activity. However, when administered intravenously to opioid dependent persons, the presence of naloxone in SUBOXONE FILM produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Clinical Trials

Efficacy of buprenorphine in combination with naloxone was demonstrated with SUBOXONE TABLETS. No clinical efficacy studies have been conducted with SUBOXONE FILM.

All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive opioid dependence treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

Clinical pharmacology studies on SUBOXONE TABLETS demonstrate an aversive effect if SUBOXONE TABLETS are misused by the injection route by opioid dependent patients.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuronidation in the small intestine and the liver. The use of SUBOXONE FILM by the oral route is therefore inappropriate. SUBOXONE FILMS are for sublingual and/or buccal administration. Table 7 shows the pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after administration of SUBOXONE FILM in randomised, crossover studies. Overall, there was wide variability in the sublingual absorption of buprenorphine and naloxone. SUBOXONE FILM and SUBOXONE TABLET do not meet all criteria for bioequivalence. Patients being switched between tablets and soluble films may therefore require dosage adjustment (see Dosage and Administration).

In several pharmacokinetic studies following the administration of different dosages, a dose of one or two of the 2 mg/0.5 mg SUBOXONE FILMS administered sublingually or buccally showed comparable relative bioavailability to the same total dose of SUBOXONE TABLETS. In contrast, one 8 mg/2 mg and one 12 mg/3 mg SUBOXONE FILM administered sublingually or buccally showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE TABLETS. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE FILMS (total dose of 12 mg/ 3 mg) administered sublingually showed comparable relative bioavailability to the same total dose of SUBOXONE TABLETS, while buccally administered SUBOXONE FILMS showed higher relative bioavailability. Table 8 below, illustrates the relative increase in exposure to buprenorphine and naloxone associated with SUBOXONE FILMS compared to SUBOXONE TABLETS and shows the effect of route of administration.

Table 7. Pharmacokinetic parameters (Mean ± SD) of buprenorphine and naloxone following SUBOXONE FILM administration

PK Parameter	SUBOXONE Film Dose (mg)			
	2 mg/0.5 mg	4 mg / 1 mg	8 mg / 2 mg	12 mg / 3 mg
Buprenorphine				
C_{max} (ng/mL)	0.947 ± 0.374	1.40 ± 0.687	3.37 ± 1.80	4.55 ± 2.50
T_{max} (h) Median, (min-max)	1.53 (0.75 - 4.0)	1.50 (0.5, 3.0)	1.25 (0.75 - 4.0)	1.50 (0.5, 3.0)

AUC_{inf} (ng.hr/mL)	8.654 ± 2.854	13.71 ± 5.875	30.45 ± 13.03	42.06 ± 14.64
$t_{1/2}$ (hr)	33.41 ± 13.01	24.30 ± 11.03	32.82 ± 9.81	34.66 ± 9.16
Norbuprenorphine				
C_{max} (ng/mL)	0.312 ±0.140	0.617 ±0.311	1.40 ±1.08	2.37 ±1.87
T_{max} (h) Median, (min-max)	1.38 (0.5 - 8.0)	1.25 (0.5, 48.0)	1.25 (0.75 - 12.0)	1.25 (0.75, 8.0)
AUC_{inf} (ng.hr/mL)	14.52 ±5.776	23.73 ±10.60	54.91 ±36.01	71.77 ±29.38
$t_{1/2}$ (hr)	56.09 ±31.14	45.96 ±40.13	41.96 ±17.92	34.36 ±7.92
Naloxone				
C_{max} (ng/mL)	0.054 ± 0.023	0.0698 ± 0.0378	0.193 ± 0.091	0.238 ± 0.144
T_{max} (h) Median, (min-max)	0.75 (0.5 - 2.0)	0.75 (0.5, 1.5)	0.75 (0.5 - 1.25)	0.75 (0.50, 1.25)
AUC_{inf} (ng.hr/mL)	0.137 ± 0.043	0.204 ± 0.108	0.481 ± 0.201	0.653 ± 0.309
$t_{1/2}$ (hr)	5.00 ± 5.52	3.91 ± 3.37	6.25 ± 3.14	11.91 ± 13.80

Table 8. Changes in Pharmacokinetic Parameters for SUBOXONE FILM Administered Sublingually or Buccally in Comparison to SUBOXONE TABLET

Dosage	PK Parameter	**Increase in Buprenorphine**			PK Parameter	**Increase in Naloxone**		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 x 2 mg/0.5 mg	C_{max}	22%	25%	-	C_{max}	-	-	-
	$AUC_{0\text{-}last}$	-	19%	-	$AUC_{0\text{-}last}$	-	-	-
2 x 2 mg/0.5 mg	C_{max}	-	21%	21%	C_{max}	-	17%	21%
	$AUC_{0\text{-}last}$	-	23%	16%	$AUC_{0\text{-}last}$	-	22%	24%
1 x 8 mg/2 mg	C_{max}	28%	34%	-	C_{max}	41%	54%	-
	$AUC_{0\text{-}last}$	20%	25%	-	$AUC_{0\text{-}last}$	30%	43%	-
1 x 12 mg/3 mg	C_{max}	37%	47%	-	C_{max}	57%	72%	9%
	$AUC_{0\text{-}last}$	21%	29%	-	$AUC_{0\text{-}last}$	45%	57%	-
1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg	C_{max}	-	27%	13%	C_{max}	17%	38%	19%
	$AUC_{0\text{-}last}$	-	23%	-	$AUC_{0\text{-}last}$	-	30%	19%

Note: 1. '–' represents no change when the 90% confidence intervals for the geometric mean ratios of the C_{max} and $AUC_{0\text{-}last}$ values are within the 80% to 125% limit. 2. There is no data for the 4 mg/1 mg strength

film; it is compositionally proportional to 2 mg/0.5 mg strength film and has the same size of 2 x 2 mg/0.5 mg film strength.

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours). Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around 4 minutes).

Buprenorphine is highly lipophilic which leads to rapid penetration of the blood-brain barrier. The medicine is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism

In animals and man buprenorphine is metabolised by Phase 1 (oxidative) and Phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. In *in vitro* metabolic studies, addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine (see also section 4.4 Special Warnings and Precautions for Use and section 4.5 Interactions). There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

Naloxone undergoes direct glucuroconjugation to naloxone-3-glucuronide as well as N-dealkylation and reduction of the 6-oxo group.

Excretion

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase (refer to Table 1), due in part to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite and in part to the highly lipophilic nature of the molecule. Naloxone has a short elimination half-life (refer to Table 7).

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine. Naloxone is excreted in the urine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In genotoxicity studies using buprenorphine and naloxone (9:2), assays for bacterial gene mutations and chromosomal damage (human lymphocytes *in vitro* and rat micronucleus test *in vivo*) were negative.

Carcinogenicity

In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100 mg/kg/day, which equates to *ca* 14-fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.

In rats, statistically significant (trend test adjusted for survival) dose-related increases in testicular interstitial (Leydig) cell tumours occurred at a dietary buprenorphine dose of 55 mg/kg/day (16 fold the maximal recommended human sublingual dose of 32 mg, on a mg/m^2 basis); the no-effect dose was 5.4 mg/kg/day (twice the maximal human dose, on a mg/m^2 basis). The carcinogenic potential of naloxone alone has not been investigated in long term animal studies.

In a 2-year dietary study with SUBOXONE TABLETS in rats, Leydig cell adenomas were found at doses of 6-115 mg/kg/day, associated with respective exposures (plasma AUC) to buprenorphine and naloxone of 2-21 fold, and up to 58 fold, anticipated human exposure. A NOEL was not established in the study.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each soluble film contains acesulfame potassium, citric acid, maltitol, hypromellose, polyethylene oxide, sodium citrate, Natural Lime Flavour 3000180, Sunset Yellow FCF and OPACODE WB monogramming ink NS-78-18007 White.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

18 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Each soluble film is packed in an individual child resistant polyethylene terephthalate (PET)/low density polyethylene (LDPE)/aluminium/LDPE sachet. There are 28 sachets in a pack.

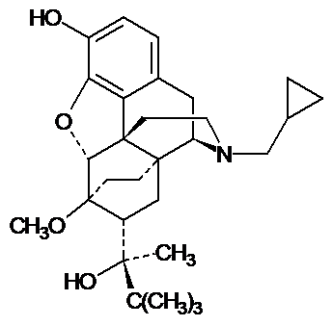
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

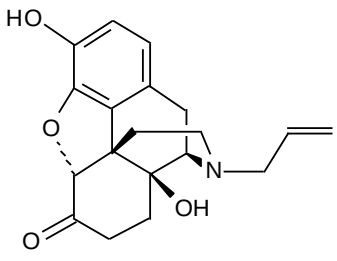
Chemical structure

The chemical structures of buprenorphine hydrochloride and naloxone hydrochloride dihydrate are:



.HCl

Buprenorphine hydrochloride



.HCl. $2H_2O$

Naloxone hydrochloride dihydrate

CAS number

The CAS number of buprenorphine hydrochloride is 53152-21-9.

The CAS number of naloxone hydrochloride dihydrate is 51481-60-8.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 - Controlled Drug

8 SPONSOR

Indivior Pty Ltd
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9 DATE OF FIRST APPROVAL

2 November 2000

10 DATE OF REVISION

29 March 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformat of PI
4.2 4.3 4.6	Removal of pregnancy and lactation from contraindications and changes to dose and method of administration
6.1	Updated excipient names to align with International Harmonisation of Ingredient Names (IHIN)
4.4 4.5	Respiratory Depression – addition of sleep apnoea Opioid withdrawal effects – addition of warning on abrupt discontinuation Addition of serotonergic drugs
6.3 6.5	Extension of shelf-life to 18 months Removal of alternative packaging type
4.4	TGA Review of prescription opioids – addition of black box warning Addition of information on hazardous and harmful use, life-threatening respiratory depression and concomitant use of benzodiazepines and other CNS depressants.