**AUSTRALIAN PRODUCT INFORMATION**

**SUBUTEX (BUPRENORPHINE)**

**WARNINGS**

***Hazardous and harmful use***

Although SUBUTEX 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 SUBUTEX (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 SUBUTEX. 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 SUBUTEX.

## 1 NAME OF THE MEDICINE

SUBUTEX sublingual tablets contain buprenorphine (as hydrochloride)

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SUBUTEX is available in three dosage strengths, 0.4 mg, 2 mg and 8 mg buprenorphine (as hydrochloride).

*Excipients with known effect*

SUBUTEX contains lactose monohydrate and mannitol.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg/mL at 37°C, pH 4.1). Chemically, buprenorphine is 21-Cyclopropyl-7α-[(S)–1-hydroxy1,2,2-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.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

SUBUTEX is an uncoated tablet intended for sublingual administration.

SUBUTEX is supplied as white, oval tablets containing 0.4 mg, 2 mg and 8 mg buprenorphine. Tablets are debossed with either "04", "B2" or "B8" respectively for SUBUTEX 0.4 mg, SUBUTEX 2 mg and SUBUTEX 8 mg.

# 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 SUBUTEX is intended for adults and children aged 16 years or over who have agreed to be treated for opioid dependence. When initiating SUBUTEX treatment, the physician should be aware of the partial agonist profile of the molecule to the μ opioid receptor, 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.

The route of administration of SUBUTEX is sublingual. The sublingual formulation is not designed to be split or broken. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug.

**Method of Administration**

SUBUTEX should be placed under the tongue until dissolved. This usually occurs within 2 to 10min. Patients should not swallow or consume food or drink until the tablet is completely dissolved. A dose is made up from SUBUTEX 2 mg and SUBUTEX 8 mg, which may be placed sublingually all at the same time or in two divided portions; the second portion to be placed sublingually directly after the first portion has dissolved.

**Starting SUBUTEX**

Following treatment induction, the patient should be rapidly stabilised on an adequate maintenance dose by titrating to clinical effect. An adequate maintenance dose holds the patient in treatment and suppresses opioid withdrawal effects and is guided by reassessment of the clinical and psychological status of the patient.

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. 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 SUBUTEX 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 SUBUTEX 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 SUBUTEX. 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 SUBUTEX, the maintenance dose of methadone should be reduced to the minimum daily dose that the patient can tolerate. The first dose of SUBUTEX should be taken at least 24 hours after the patient last used methadone. An initial dose of 2 mg SUBUTEX may be administered when moderate withdrawal is apparent (COWS ≥ 13). An additional dose of 6 mg SUBUTEX 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 SUBUTEX. A maximum daily dose of 32 mg should not be exceeded.

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

**Dose adjustment in hepatic impairment**

In patients with severe hepatic impairment, consider reducing the starting and titration doses by half compared to patients with normal liver function, and monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

No dose adjustment is necessary for patients with moderate hepatic impairment, although SUBUTEX should be used with caution in these patients. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

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

**Dosage Adjustment and Maintenance**

The dose of SUBUTEX should be increased 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***

For patients who require supervised dosing, a less-than daily dosing regimen may facilitate supervised dosing in patients with opioid dependence that is uncomplicated by concomitant dependence on other agents with central nervous system (CNS) activity, including alcohol.

After a satisfactory stabilisation has been achieved, the frequency of dosing may be decreased to 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, three times a week (for example on Monday, Wednesday and Friday) may be used. The dose on Monday and Wednesday may be twice the daily dose, and the dose on Friday may be three times the individually titrated daily dose. 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 SUBUTEX should be made as part of a comprehensive treatment plan. A gradual dose taper over a period of 21 days is shown in Table 1.

| **Table 1** | **Gradual dose taper schedule** | | |
|---|---|---|---|
| Week | Maintenance dose | | |
| 0 | 20 mg | 16 mg | 8 mg |
| 1 | 16 mg | 12 mg | 8 mg |
| 2 | 8 mg | 8 mg | 4 mg |
| 3 | 4 mg | 4 mg | 4 mg |

**Detoxification**

Examples of two 10-day detoxification schedules using SUBUTEX are shown in Tables 1 and 2. These have been used to treat subjects who wish to stop using heroin and do not want to undergo a prolonged period of maintenance treatment on SUBUTEX.

In the first detoxification schedule heroin dependent subjects are transferred to SUBUTEX at doses up to 8 mg/day. The dose of buprenorphine was gradually decreased in a flexible 10-day schedule (Table 2).

| **Table 2** | **Detoxification Schedule 1** |
|---|---|
| DAY | SUBUTEX (mg) |
| 1 | 8 |
| 2 | 6 |
| 3 | 6 |
| 4 | 4 |
| 5 | 4 |
| 6 | 2 |
| 7 | 2 |
| 8 | 1 |
| 9 | 1 |
| 10 | 0 |

A similar schedule employed SUBUTEX treatment only on the first 5 days (Table 3). The SUBUTEX dose was increased over the first 3 days and then decreased.

| **Table 3** | **Detoxification Schedule 2** |
|---|---|
| DAY | SUBUTEX (mg) |
| 1 | 6 |
| 2 | 10 +/- 2 |
| 3 | 10 +/- 2 |
| 4 | 8 +/- 2 |
| 5 | 4 |

## 4.3 CONTRAINDICATIONS

Hypersensitivity to buprenorphine or any other component of the tablet.
Children less than 16 years of age.
Severe respiratory insufficiency.
Acute intoxication with alcohol or other CNS depressant.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### General

SUBUTEX should be administered with caution in debilitated patients and those with severe 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 SUBUTEX 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 SUBUTEX 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 SUBUTEX 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 SUBUTEX.

SUBUTEX 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. SUBUTEX 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. Sub-optimal treatment with buprenorphine may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines. To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX, 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 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 SUBUTEX. Be aware of situations which increase the risk of respiratory depression and monitor patients closely, especially on initiation or following a dose increase.

SUBUTEX is intended for sublingual use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines, when high dose buprenorphine was administered to nonopioid dependent individuals who had not developed a tolerance to the effects of opioids, 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 CNS 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 SUBUTEX.

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

SUBUTEX may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

SUBUTEX 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, or pre-existing respiratory depression or kyphoscoliosis).

Patients with the physical and or pharmacological risk factors above should be monitored, and dose reduction may be considered.

**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 SUBUTEX.

SUBUTEX 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, and 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 SUBUTEX 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 with other medicines) 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 is extensively metabolised by the liver. The effects of hepatic impairment on the pharmacokinetics of buprenorphine 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 in patients with moderate to severe hepatic impairment (Table 4) which may require dose adjustment. Buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function.

Buprenorphine should be used with caution in patients with moderate to severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Lower initial doses and cautious titration of dosage may be required in patients with severe hepatic impairment (see section 4.2 Dose and Method of Administration).

**Table 4: Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine 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** | | | |
| **Cmax** | **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** |

In the same study, changes in Cmax and AUClast 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 SUBUTEX. 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 (CLcr <30 ml/min), which may require dose adjustment.

**Head Injury and Increased Intracranial Pressure**

SUBUTEX, like other potent opioids may itself elevate cerebrospinal fluid pressure 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. SUBUTEX can produce miosis and changes in the level of consciousness, or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

**Opioid Withdrawal Effects**

SUBUTEX 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 showed that buprenorphine may produce dependence but at a lower level than a full agonist (e.g. morphine). Consequently, it is

important to follow the DOSE AND METHOD OF ADMINISTRATION recommendations. 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, convulsions, apnoea 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 is a contraindication to SUBUTEX.

**Paediatric Use**

SUBUTEX is not recommended for use in children. The safety and effectiveness of SUBUTEX in subjects below the age of 16 has not been established. Due to limited amount of available data, patients below the age of 18 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. SUBUTEX is not appropriate as an analgesic.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Alcohol**

Increases the sedative effect of buprenorphine. SUBUTEX should not be used 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 in cases 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 machines hazardous.

Examples of central nervous system depressants are: other 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).

**Other opioid analgesics**

The analgesic properties of other opioids such as methadone and level III analgesics may be reduced in patients receiving treatment with buprenorphine for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. 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 SUBUTEX. Patients maintained on SUBUTEX tablets 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 Cmax and AUC of buprenorphine (approximately 50%and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBUTEX 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 SUBUTEX should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, and rifampicin) are co-administered and the dose of buprenorphine or CYP3A4 inducer may need to be adjusted accordingly.

**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 on fertility of male rats following short term treatment with buprenorphine at systemic exposures up to 38 times the maximum anticipated human exposure (based on plasma AUC).

### Use in Pregnancy - Pregnancy Category C

Treatment with buprenorphine during pregnancy was associated with difficult parturition and fetotoxicity, including post-implantation loss and decreased post-natal survival, in rats and rabbits at systemic exposures similar to the maximum anticipated human exposure (32 mg/day). Evidence for teratology was not evident in animal studies.

Maternal oral administration at high doses (80mg/kg/day) during gestation and lactation resulted in a delayed postnatal development of some neurological functions (surface righting reflex and startle response) in neonatal rats with a NOEL of 8mg/kg/day PO (representing a systemic exposure of ~30% of the maximum anticipated clinical exposure).

Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

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 (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Buprenorphine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. 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. Decreases in postnatal survival, growth and development were also observed in animals treated with buprenorphine during lactation. 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 passes into the mother's milk, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBUTEX and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Buprenorphine may influence the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used 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 with other medicines). Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events reported to occur by at least 1% of patients being treated in clinical trials of SUBUTEX (CR96/005 and CR96/013) are shown in Table 5. The frequency of possible side effects listed below is defined using the following convention: Very common (≥1/10), Common (≥1/100 to <1/10).

**Table 5. Treatment-related undesirable effects reported by body system in clinical studies of buprenorphine [SUBUTEX]**

| *System Organ Class* | **Very common (≥1/10)** | **Common (≥1/100 to <1/10)** |
|---|---|---|
| *Infections and infestations* | | Bronchitis<br>Infection<br>Influenza<br>Pharyngitis<br>Rhinitis |
| *Blood and lymphatic system disorders* | | Lymphadenopathy |
| *Metabolism and nutrition disorders* | | Decreased appetite |
| *Psychiatric disorders* | Insomnia | Agitation<br>Anxiety<br>Depression<br>Hostility<br>Nervousness<br>Paranoia<br>Thinking abnormal |
| *Nervous system disorders* | Headache | Dizziness<br>Hypertonia<br>Migraine<br>Paraesthesia<br>Somnolence<br>Syncope<br>Tremor |
| *Eye disorders* | | Lacrimal disorder<br>Mydriasis |
| *Cardiac disorders* | | Palpitations |
| *Vascular disorders* | | Vasodilatation |
| *Respiratory, thoracic and mediastinal disorders* | | Cough<br>Dyspnoea<br>Yawning |
| *Gastrointestinal disorders* | Nausea | Abdominal pain<br>Constipation<br>Diarrhoea<br>Dry mouth<br>Dyspepsia<br>Gastrointestinal disorder<br>Flatulence<br>Tooth disorder<br>Vomiting |
| *Skin and subcutaneous tissue disorders* | Hyperhidrosis | Rash |

| Table 5. Treatment-related undesirable effects reported by body system in clinical studies of buprenorphine [SUBUTEX] | | |
|---|---|---|
| *System Organ Class* | **Very common (≥1/10)** | **Common (≥1/100 to <1/10)** |
| *Musculoskeletal, connective tissue and bone disorders* | | Arthralgia<br>Back pain<br>Bone pain<br>Muscle spasms<br>Myalgia<br>Neck pain<br>Leg cramps |
| *Reproductive system and breast disorders* | | Dysmenorrhoea |
| *General disorders and administration site conditions* | Drug withdrawal syndrome<br>Pain | Asthenia<br>Chest pain<br>Chills<br>Malaise<br>Oedema peripheral<br>Pyrexia |

The most common adverse events reported were those related to withdrawal symptoms (e.g. abdominal pain, headache, pain, diarrhoea, nausea, 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.

**Post-marketing experience with SUBUTEX**

Post-marketing experience with SUBUTEX for treatment of opioid dependence 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, , orthostatic hypotension, heart rate and rhythm disorders, and deaths.

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

In cases of intravenous or intentional misuse, local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections have been reported.

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

## 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 SUBUTEX 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 further information on the management of overdose, contact the Poison Information Centre on 131126 (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.

### Clinical Trials

Efficacy and safety data for SUBUTEX are primarily derived from two clinical trials of sublingual tablets (Studies CR96/005 and CR96/013). 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.

***Study CR96/005***: In a double-blind, double dummy, flexible dose-ranging, parallel group, comparative, 13-week study, 405 opioid dependent subjects were randomised to receive daily SUBUTEX sublingual tablets or methadone syrup. During Weeks 1-6, doses were individually titrated until a stable dose was achieved (to a maximum of 32 mg SUBUTEX or 150 mg methadone). Induction over 7 days was too slow for SUBUTEX and resulted in early drop-outs. Once an adequate clinical dose of SUBUTEX was attained it was maintained. During Weeks 1-6, the most used daily dose of SUBUTEX was 8 mg/day and the average prescribed dose of buprenorphine in Week 6 was 10.9 mg/day. During Weeks 7-13 SUBUTEX was dosed on alternate days by doubling the daily dose, with placebo tablets administered on intervening days. The most used SUBUTEX dose during this phase was 16 mg given every other day. Methadone was dosed daily throughout the study with the most used doses being 40 mg/day in Weeks 1-6 and 50 mg/day in Weeks 7-13. The average prescribed dose of methadone in Week 6 was 53 mg/day. Take home doses were not permitted except on weekends. Daily or alternate day SUBUTEX had similar efficacy to daily methadone. In both parts of the study there were no differences between the groups in the percentages of urine samples that were negative for opioids. The secondary

efficacy parameters complemented the results of the primary parameters. Heroin use and heroin craving were reduced in both treatment groups and other measures reflecting problems associated with illicit opioid use also improved with treatment and there were no treatment group differences overall and in the two phases of the study.

***Study CR96/013***: In a double-blind, multicentre, placebo-controlled study, 326 heroin dependent subjects were randomly assigned to either placebo, SUBUTEX 16 mg/day, or combination treatment of 16 mg buprenorphine + 4 mg naloxone (combination tablet) per day. For subjects randomised to active treatment, dosing began with one 8 mg tablet of SUBUTEX on Day 1, followed by 16 mg (two 8 mg tablets) of SUBUTEX on day 2. Subjects randomised to SUBUTEX continued on 16 mg/day for four weeks. Subjects randomised to buprenorphine + naloxone were switched to the combination tablet on Day 3. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take home doses were permitted for the weekend or holidays only. Subjects received one hour of individual counselling per week and a single session of HIV education. The percentage of thrice-weekly urine samples that were negative for opioids was significantly higher for subjects treated with SUBUTEX or the combination tablet than for those who received placebo.

## 5.2 PHARMACOKINETIC PROPERTIES

### Absorption

When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of SUBUTEX by the oral route is therefore inappropriate. SUBUTEX tablets are for sublingual administration.

Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX although the increases were not directly dose-proportional (Table 6). There was a wide inter-patient variability in the sublingual absorption of buprenorphine from SUBUTEX tablets, but within subjects the variability was low.

**Table 6** **Mean $C_{max}$ \UC of buprenorphine following single sublin SUBUTEX tablets in 23 (16M, 7F) subjects.**

| | 4 mg SUBUTEX | 8 mg SUBUTEX | 16 mg SUBUTEX | 24 mg SUBUTEX |
|---|---|---|---|---|
| $C_{max}$ ng/mL | 2.00 (0.31-3.76) | 2.65 (1.09-4.82) | 4.42 (1.79-8.58) | 5.41 (1.67-17.3) |
| $AUC_{0\text{-}tn}$ h.ng/mL | 9.37 (2.11-24.64) | 19.92 (6.19-64.81) | 34.94 (9.25-101.6) | 48.81 (15.7-135) |

Compared with intravenous administration, the bioavailability of 0.4mg and 0.8mg sublingual buprenorphine tablet doses was 30-35%. With 8mg sublingual buprenorphine delivered as a solution the buprenorphine bioavailability compared to intravenous administration was 42%.

### Distribution

The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours).

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.

### Metabolism and elimination

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. The reported Km for buprenorphine for CYP 3A4 in human liver microsomes was 89 mM, and addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine. There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the Ndealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4 (reported mean Ki in human liver microsomes was 10.3 μM and 40.2 μM respectively). Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase (mean half-life of 34.6 hours, range 20.4-72.9 hours), 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.

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

### 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

The conclusion from Ames tests, chromosome aberration studies and a mouse lymphoma assay is that buprenorphine is not mutagenic in any of these test systems.

**Carcinogenicity**

Studies conducted in animals (rats and mice) show that buprenorphine is not carcinogenic at oral doses of up to 56 and 100 mg/kg/day, respectively, both of which equate to approximately 16 fold human exposure at the maximum recommended clinical dose of 32 mg based on body surface area.

## 6 PHARMACEUTICAL PARTICULARS

#### 6.1 LIST OF EXCIPIENTS

Each tablet contains lactose monohydrate, mannitol, starch-maize, povidone, citric acid, sodium citrate dihydrate, and magnesium stearate.

#### 6.2 INCOMPATIBILITIES

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

#### 6.3 SHELF LIFE

| | |
|---|---|
| Blister packs | 3 years |
| Jars | 2 years |

#### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from prolonged exposure to light. Protect from moisture. Keep out of reach of children.

#### 6.5 NATURE AND CONTENTS OF CONTAINER

SUBUTEX is packed in Al/Al blister packs of 28* or 7 sublingual tablets and jars of 100* sublingual tablets*. * not supplied

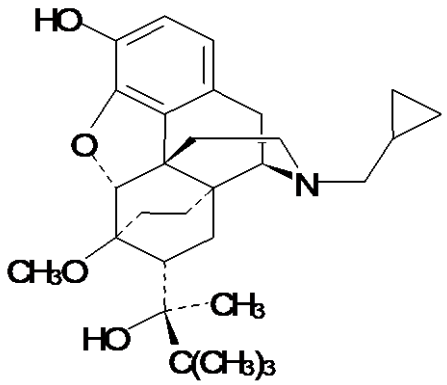
#### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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 structure of buprenorphine is:




**CAS number**

The CAS number is 53152-21-9

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 - Controlled Drug

## 8 SPONSOR

Indivior Pty Ltd
78 Waterloo Road
Macquarie Park NSW 2113
Australia

For adverse event reporting please contact:
Indivior Pty Ltd
+800-270-81901
PatientSafetyRoW@indivior.com

## 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<br>4.3<br>4.6 | Removal of pregnancy and lactation from contraindications and changes to dose and method of administration |
| 4.4<br><br>4.5 | Respiratory Depression – addition of sleep apnoea<br>Opioid withdrawal effects – addition of warning on abrupt discontinuation<br>Addition of serotonergic drugs |
| 4.4 | TGA Review of prescription opioids – addition of black box warning<br>Addition of information on hazardous and harmful use, life-threatening respiratory depression and concomitant use of benzodiazepines and other CNS depressants. |