SUBUTEX (buprenorphine)

0.4mg, 2mg and 8mg Sublingual Tablets

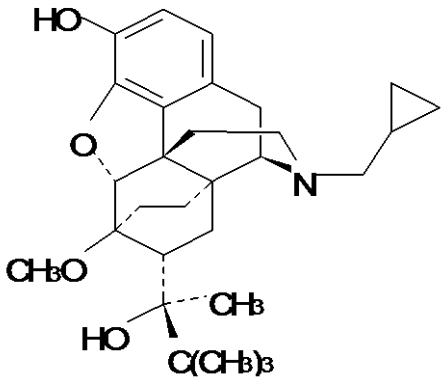
NAME OF THE MEDICINE

SUBUTEX sublingual tablets contain buprenorphine hydrochloride.

DESCRIPTION

SUBUTEX is an uncoated tablet intended for sublingual administration. It is available in three dosage strengths, 0.4mg, 2mg and 8mg buprenorphine. Each tablet also contains lactose, mannitol, starch-maize, povidone, citric acid-anhydrous, sodium citrate, and magnesium stearate.

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- 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. The chemical structure of buprenorphine is:



PHARMACOLOGY

Pharmacodynamic properties

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.

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 1). There was a wide inter-patient variability in the sublingual absorption of buprenorphine from SUBUTEX tablets, but within subjects the variability was low.

Table 1.	Mean C_{max} and AUC of buprenorphine following single sublingual doses of 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-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 K_m 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 N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4 (reported mean K_i 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.

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.

INDICATIONS

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

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.
Pregnant Women.
Breast feeding.

PRECAUTIONS

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.

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

Misuse, abuse and diversion: 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.

Respiratory Depression*:* 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 non-opioid 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 OVERDOSAGE.

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, 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*:* SUBUTEX may cause drowsiness, particularly when used together with alcohol or central nervous system depressants (such as benzodiazepines, tranquillisers, sedatives or hypnotics). When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. 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 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.

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 2). 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 DOSAGE AND ADMINISTRATION).

Table 2: 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 C_{max} and AUC_{last} in subjects with HCV infection without hepatic impairment were not clinically significant in comparison to the healthy subjects.

Renal Disease*:* 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 (CL_{cr} <30 ml/min), which may require dose adjustment.

Effects on ability to drive and use machinery*:* 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 PRECAUTIONS and 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.

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. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed. Buprenorphine is a partial agonist at the μ (mu)-

opiate 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 DOSAGE AND ADMINISTRATION recommendations.

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 *Use in Pregnancy*).

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.

Carcinogenicity & Mutagenicity
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.

Mutagenicity: 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.

Impairment of 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 (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.

There are no adequate and well controlled studies of SUBUTEX in pregnant women. 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.

SUBUTEX is contraindicated in pregnant women (see CONTRAINDICATIONS).

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. Because buprenorphine passes into the mother's milk, SUBUTEX should not be used in breast-feeding women.

Use in Children
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.

INTERACTIONS WITH OTHER MEDICINES

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 PRECAUTIONS).

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 PRECAUTIONS).

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), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine and related substances.

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 PRECAUTIONS).

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 C_{max} 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.

ADVERSE 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 3. 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 3. 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 Infection Influenza Pharyngitis Rhinitis
Blood and lymphatic system disorders		Lymphadenopathy
Metabolism and nutrition disorders		Decreased appetite
Psychiatric disorders	Insomnia	Agitation Anxiety Depression Hostility Nervousness Paranoia Thinking abnormal
Nervous system disorders	Headache	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor
Eye disorders		Lacrimal disorder Mydriasis
Cardiac disorders		Palpitations
Vascular disorders		Vasodilatation
Respiratory, thoracic and mediastinal disorders		Cough Dyspnoea Yawning
Gastrointestinal disorders	Nausea	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Gastrointestinal disorder Flatulence Tooth disorder Vomiting
Skin and subcutaneous tissue disorders	Hyperhidrosis	*Rash*
Musculoskeletal, connective tissue and bone disorders		Arthralgia Back pain Bone pain Muscle spasms Myalgia Neck pain Leg cramps
Reproductive system and breast disorders		Dysmenorrhoea
General disorders and administration site conditions	Drug withdrawal syndrome Pain	Asthenia Chest pain Chills Malaise Oedema peripheral Pyrexia

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

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 PRECAUTIONS) 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 PRECAUTIONS).

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 PRECAUTIONS and CONTRAINDICATIONS).

DOSAGE AND ADMINISTRATION

Treatment with SUBUTEX sublingual tablets 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 tablets 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. The initial dose of SUBUTEX may precipitate a mild abstinence syndrome in opioid-dependent subjects. This may last up to 24 hours, but resolves with continued daily administration of SUBUTEX.

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.

Patients taking Street 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 or when the early

signs of withdrawal appear. The recommended starting dose is 4 mg SUBUTEX on day one, with a possible additional 4 mg depending on the individual patient's requirement.

Patients on Methadone: Before starting treatment with SUBUTEX, the maintenance dose of methadone should be reduced to 30 mg per day. The first dose of SUBUTEX should be taken at least 24 hours after the patient last used methadone. The initial 4mg SUBUTEX induction dose should ideally be administered when the early withdrawal signs are evident.

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 sublingual tablets 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 and should not exceed a maximum daily dose of 32 mg. The dosage is adjusted according to reassessments of the clinical and psychological status of the patient.

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 4.

Table 4 Gradual dose taper schedule

Week	Maintenance dose		
0	20mg	16mg	8mg
1	16mg	12mg	8mg
2	8mg	8mg	4mg
3	4mg	4mg	4mg

Detoxification

Examples of two 10-day detoxification schedules using SUBUTEX are shown in Tables 4 and 5. 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 5).

Table 5 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 6). The SUBUTEX dose was increased over the first 3 days and then decreased.

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

OVERDOSAGE

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

In the event of accidental overdose, general supportive measures should be instituted including close monitoring of respiratory and cardiac status of the patient. 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).

PRESENTATION AND STORAGE CONDITIONS

SUBUTEX is supplied as white, oval tablets containing 0.4mg, 2mg and 8mg buprenorphine. Tablets are debossed with either “04”, “B2” or “B8” respectively for SUBUTEX 0.4mg, SUBUTEX 2mg and SUBUTEX 8mg.
SUBUTEX is packed in Al/Al blister packs of 28* or 7 sublingual tablets, and jars of 100* sublingual tablets*.
* not supplied

Store below 30^{o}C. Protect from prolonged exposure to light. Protect from moisture. Keep out of reach of children.

NAME AND ADDRESS OF THE 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

POISON SCHEDULE OF THE MEDICINE
Schedule 8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)
2 November 2000

DATE OF MOST RECENT AMENDMENT

16 August 2016