NEW ZEALAND DATA SHEET

WARNINGS

Hazardous and harmful use

Although SUBOXONE 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 (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. 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.

1. PRODUCT NAME

SUBOXONE 2 mg/0.5 mg sublingual tablet

SUBOXONE 8 mg/2 mg sublingual tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet of SUBOXONE 2 mg/0.5 mg contains 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate).
Each sublingual tablet of SUBOXONE 8 mg/2mg contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate).
Excipients with known effect: The sublingual tablets contain lactose (as monohydrate): 42 mg in each SUBOXONE 2 mg/0.5 mg and 168 mg in each SUBOXONE 8 mg/2 mg.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet
SUBOXONE 2 mg/0.5 mg: white, hexagonal, biconvex tablets debossed with a "N2".
SUBOXONE 8 mg/2 mg: white, hexagonal, biconvex tablets debossed with a "N8".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of opioid dependence, within a framework of medical, social and psychological treatment. Naloxone is included in SUBOXONE to deter intravenous misuse of the product.

4.2 Dose and method of administration

Treatment with SUBOXONE sublingual tablets is intended for adults and children aged 16 years or

over who have agreed to be treated for opioid dependence. When initiating SUBOXONE 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.

The route of administration of SUBOXONE is sublingual. The sublingual formulation is not designed to be split or broken. SUBOXONE tablets should not be swallowed as this reduces the bioavailability of the medicine. Physicians must advise patients that the sublingual route is 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

Suboxone tablets are to be placed under the tongue until dissolved, which usually requires 2 to 10 minutes. Patients should not swallow or consume food or drink until the tablet is completely dissolved. The dose is made up from 2 mg and 8 mg sublingual tablets, which may be taken all at the same time or in two divided portions; the second portion to be taken directly after the first portion has dissolved.

Starting SUBOXONE

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.

Patients taking Heroin (or Other Short-acting Opioids): When treatment starts the dose of SUBOXONE should be taken at least 6 hours after the patient last used opioids and when objective signs of withdrawal appear. A score of 12 on the validated Clinical Opioid Withdrawal Scale (COWS) may be a useful reference assessment. The recommended starting dose is 4-8 mg SUBOXONE 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.

Patients on Methadone: Before starting treatment with SUBOXONE, the maintenance dose of methadone should be reduced to the minimum methadone daily dose that the patient can tolerate. The first dose of SUBOXONE should be taken at least 24 hours after the patient last used methadone. The initial 4-8 mg SUBOXONE induction dose should ideally be administered when objective signs of withdrawal are evident (e.g. COWS score > 12). The suggested target total dose for Day One is in the range of 8-12 mg SUBOXONE.

During the initiation of treatment, closer 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.

Dosage Adjustment and Maintenance

The dose of SUBOXONE 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.

In clinical studies many patients were stabilised on a daily maintenance dose of 12 mg/3 mg to 16 mg/4 mg of SUBOXONE, although some patients may require higher doses. A maximum daily dose of 32 mg should not be exceeded. During maintenance therapy, it may be necessary to periodically restabilise patients to new maintenance doses in response to changing patient needs.

Dose adjustment in hepatic impairment

Use of SUBOXONE is contraindicated in patients were severe hepatic impairment. SUBOXONE may not be appropriate for patients with moderate hepatic impairment. SUBOXONE 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.

Less than Daily Dosing of SUBOXONE

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 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	**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 tablet.

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 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 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.

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

Opioids may produce orthostatic hypotension in ambulatory patients.

Use in the elderly

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

Misuse, abuse and diversion

Although SUBOXONE 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.

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. 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 the risk of misuse, abuse and 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 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. Be aware of situations which increase the risk of respiratory depression and monitor patients closely, especially on initiation or following a dose increase.

SUBOXONE is intended for sublingual 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.

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

SUBOXONE 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 may cause severe, possibly 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.

SUBOXONE 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 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 buprenorphine/naloxone 2mg/0.5 mg 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 it 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 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).

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			
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
NALOXONE			
Cmax	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, 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 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 contains naloxone, it is highly likely to produce marked and intense opioid withdrawal symptoms if injected.

SUBOXONE 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 chronic administration produces dependence of the opioid type, but at a lower level than a full agonist (e.g. morphine). The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset. Consequently, it is important to follow the recommendations in section 4.2.

Withdrawal symptoms may also be associated with sub-optimal dosing.

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*). 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.

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 use.

Use in children:

SUBOXONE is not recommended for use in children. The safety and effectiveness of SUBOXONE in subjects below the age of 16 has not been established. Due to the limited amount of available data, patients below the age of 18 years 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 naïve individuals who received doses as low as 2 mg of buprenorphine sublingual tablet for analgesia. SUBOXONE is not appropriate as an analgesic.

4.5 Interaction with other medicines and other forms of interaction

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 *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 *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 hazardous. Examples include opioids (e.g. methadone, analgesics, antitussives), gabapentinoids, cannabis, certain antidepressants, antihistamines (e.g. sedating H1-receptor antagonists), barbiturates, anxiolytics, neuroleptics and clonidine (see *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 *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. Patients maintained on sublingual SUBOXONE 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 SUBOXONE 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 should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category C)

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.

SUBOXONE should be used during pregnancy only if the potential benefits 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.

Breast-feeding

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. 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 and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Fertility

There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses ca 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2). Dietary administration of SUBOXONE 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.

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 or dose adjustment. If used together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see *4.4 Special Warnings and Precautions for Use* and *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 Undesirable effects

Table 3 summarises adverse reactions reported from pivotal clinical studies in which, 342 of 472 patients (72.5%) reported adverse reactions. The frequency of possible side effects listed below is defined using the following convention: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000).

Table 3: Treatment-related adverse reactions reported in clinical studies

Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**
Infections and infestations		
	Influenza Infection Pharyngitis Rhinitis	Urinary tract infection Vaginal infection
Blood and lymphatic system disorders		
		Anaemia Thrombocytopenia Leukopenia Lymphadenopathy Leukocytosis
Immune system disorders		
		Hypersensitivity
Metabolism and nutrition disorders		
	Decreased appetite	Hyperglycaemia Hyperlipidaemia Hypoglycaemia
Psychiatric disorders		
Insomnia	Anxiety Nervousness Depression Libido decreased Thinking abnormal	Agitation Drug dependence Hostility Depersonalisation Abnormal dreams Apathy Euphoric mood
Nervous system disorders		
Headache	Somnolence Dizziness Paraesthesia Hypertonia Migraine	Convulsion Tremor Hyperkinesia Speech disorder Amnesia
Eye disorders		
	Lacrimal disorder Amblyopia	Miosis Conjunctivitis

Table 3: Treatment-related adverse reactions reported in clinical studies		
Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**
Cardiac disorders		
		Myocardial infarction Angina pectoris Palpitations Tachycardia Bradycardia
Vascular disorders		
	Vasodilatation Hypertension	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Cough	Dyspnoea Asthma Yawning
Gastrointestinal disorders		
Constipation Nausea	Abdominal Pain Vomiting Dyspepsia Diarrhoea Flatulence	Mouth ulceration Tongue discolouration
Skin and subcutaneous tissue disorders		
Hyperhidrosis	Rash Pruritus Urticaria	Dermatitis exfoliative Acne Skin mass Alopecia Dry skin
Musculoskeletal and connective tissue disorders		
	Arthralgia Back Pain Myalgia Muscle spasms Leg cramps	Arthritis
Renal and urinary disorders		
	Urine Abnormality	Haematuria Nephrolithiasis Dysuria Urinary retention Albuminuria
Reproductive system and breast disorders		
	Erectile Dysfunction	Amenorrhoea Ejaculation disorder Menorrhagia Metrorrhagia
General disorders and administration site conditions		
Drug withdrawal syndrome	Asthenia Pyrexia Malaise Chills Chest Pain Pain Oedema peripheral Injury	Hypothermia Heat stroke
Investigations		
	Liver function test abnormal Weight decreased	Blood creatinine increased

The most common adverse events reported were those related to withdrawal symptoms (e.g. abdominal pain, diarrhoea, muscle aches, anxiety, sweating, insomnia, headache, constipation, nausea). In patients with marked opioid dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone. Some reports of seizure, vomiting, diarrhoea and elevated liver function tests were considered serious.

Post-marketing experience with buprenorphine alone and SUBOXONE

Post-marketing experience with buprenorphine alone has been associated with the following side effects: respiratory depression (see *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, syncope, heart rate and rhythm disorders, and deaths.

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

In cases of intravenous misuse of buprenorphine, 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, angioneurotic oedema, and anaphylactic shock (see *4.3 Contraindications* and *4.4 Special Warnings and Precautions for Use*).

The most commonly reported adverse event for SUBOXONE reported during post-marketing surveillance, are mentioned in Table 4 below. Events occurring in at least 1% of reports be healthcare professionals and considered to be at least possibly related to treatment are included. Adverse drug reactions are presented by MedDRA System Organ Class in internationally agreed order by preferred term and frequency of reporting.

Table 4: Spontaneous adverse drug reactions collected through post-marketing surveillance reported by body system - SUBOXONE

System Organ Class	**Preferred Term**
Psychiatric disorders	Anxiety
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea Vomiting
Skin and subcutaneous disorders	Rash Urticaria Hyperhidrosis
General disorders and administration site conditions	Drug withdrawal syndrome Oedema peripheral; Oedema

Additionally, post-marketing experience with SUBOXONE for treatment of opioid dependence has been associated rarely with the following side effects: insomnia, reduced feeling, anorexia, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

For adverse event reporting please contact:

Indivior Pty Ltd
+800-270-81901
PatientSafetyRoW@indivior.com

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 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 advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, drugs used in addictive disorders, ATC code: N07BC51.

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 or sublingually has no detectable pharmacological activity. However, when administered intravenously to opioid dependent persons, the presence of naloxone in SUBOXONE produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Clinical trials

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 demonstrate an aversive effect if SUBOXONE is misused by the injection route by opioid dependent patients. However, there have been no clinical trials to demonstrate a reduction in injection episodes because of the inherent difficulties and ethics in obtaining realistic outcomes of such a measure in a controlled study environment. Efficacy and safety data for SUBOXONE are primarily derived from a one-year clinical trial, comprising a 4 week randomised double blind comparison of SUBOXONE, buprenorphine and placebo tablets followed by a 48-week safety study of SUBOXONE (Study CR96/013 + CR96/014).

In the double blind placebo- and active controlled study, 326 heroin-dependent subjects were randomly assigned to either SUBOXONE 16 mg per day, 16 mg buprenorphine per day or placebo tablets. For subjects randomised to either active treatment, dosing began with one 8 mg tablet of buprenorphine on Day 1, followed by 16 mg (two 8 mg tablets) of buprenorphine on Day 2. On Day 3, those randomised to receive SUBOXONE were switched to the combination tablet. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. The primary study comparison was to assess the efficacy of buprenorphine and SUBOXONE individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both SUBOXONE versus placebo ($p < 0.0001$) and buprenorphine versus placebo ($p < 0.0001$).

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 SUBOXONE by the oral route is therefore inappropriate. SUBOXONE tablets are for sublingual administration.

Plasma levels of buprenorphine and naloxone increased with the sublingual dose of SUBOXONE although the increases were not directly dose-proportional (Table 5). The levels of naloxone were too low to determine area under the curve values. There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone from SUBOXONE tablets, but within subjects the variability was low.

Table 5. Mean Cmax and AUC of buprenorphine and naloxone following single sublingual doses of SUBOXONE tablets.

	4 mg SUBOXONE (4 mg buprenorphine + 1 mg naloxone)	**8 mg SUBOXONE (8 mg buprenorphine + 2 mg naloxone)**	**16 mg SUBOXONE (16 mg buprenorphine + 4 mg naloxone)**	**24 mg SUBOXONE (24 mg buprenorphine + 6 mg naloxone)**
Buprenorphine				
Subjects	22	22	21	12
C_{max} ng/mL	2.16 (0.68-4.33)	3.33 (1.10-6.36)	5.87 (2.48-10.0)	6.44 (3.43-10.5)
$AUC_{0\text{-}tn}$ h. ng/mL	12.88 (5.18-23.24)	22.14 (8.62-44.11)	37.67 (18.71-74.13)	47.55 (24.23-96.43)
Naloxone				
Subjects	20	21	20	12
C_{max} ng/mL	0.12 (0.06-0.25)	0.23 (0.09-0.42)	0.39 (0.07-1.15)	0.47 (0.08-1.02)

Naloxone did not affect the pharmacokinetics of buprenorphine and both SUBOXONE and buprenorphine deliver similar plasma concentrations of buprenorphine. Compared with intravenous administration, the mean absolute bioavailability of buprenorphine from sublingual SUBOXONE 8mg tablets was 13.6% (range 5.1-24.9%) and that of naloxone was approximately 3%.

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 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. 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 sections *4.4 Special Warnings and Precautions for Use* and *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.

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. Naloxone has a short elimination half-life (mean 1.1 hours, range 0.63-1.94 hours).

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

Pregnancy

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).

Breast-feeding

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. Because buprenorphine is excreted into human milk, SUBOXONE should not be used in breast-feeding women.

Fertility

There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses ca 20 times the maximum clinical dose of 32 mg/day (based on mg/m^2). Dietary administration of SUBOXONE 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.

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 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.

Mutagenicity

In genotoxic 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol
Maize starch
Povidone K 30
Citric acid
Sodium citrate dihydrate
Magnesium stearate
Acesulfame potassium
Natural lemon and lime flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

7 tablets in blister packs Paper/Aluminium/Nylon/Aluminium/PVC.
28 tablets in blister packs Paper/Aluminium/Nylon/Aluminium/PVC.
Not all pack sizes may be marketed.

The tablets are packed in aluminium / aluminium blister packs of 7 or 28 sublingual tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Controlled Drug: C4

8. SPONSOR

Pharmacy Retailing (NZ) Ltd
t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Mangere
Auckland 2022
Telephone (09) 918 5100
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9. DATE OF FIRST APPROVAL

13 January 2005

10. DATE OF REVISION OF THE TEXT

02 September 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatting to new template
4.2 4.3 4.6	Removal of pregnancy and lactation from contraindications and changes to dosage and administration section
4.5	Addition of serotonergic drugs
Black box 4.4	Addition of black box warnings Addition of information on hazardous and harmful use, life-threatening respiratory depression and concomitant use of benzodiazepines and other CNS depressants.
4.5	Remove information on serotonin syndrome