

## DATA SHEET

# SUBOXONE (buprenorphine + naloxone)

2mg/0.5mg and 8mg/2mg Sublingual Tablets

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### NAME OF THE DRUG

SUBOXONE sublingual tablets contain buprenorphine hydrochloride and naloxone hydrochloride at a ratio of 4:1 buprenorphine : naloxone.

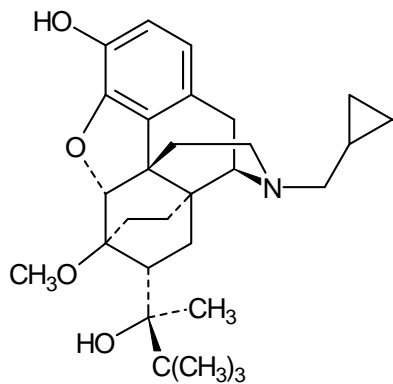
### DESCRIPTION

SUBOXONE is an uncoated tablet intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine + 0.5mg naloxone and 8mg buprenorphine + 2mg naloxone. Each tablet also contains lactose, mannitol, maize-starch, povidone, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium and Lemon & Lime flavour

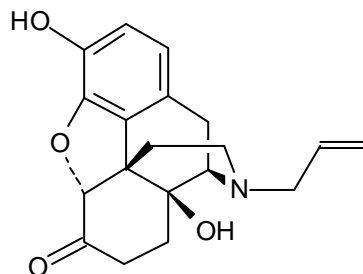
Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg /mL at 37°, pH 4.1). Chemically, it is 21-Cyclopropyl-7 $\alpha$ -[(S) -1- hydroxy-1,2,2 - trimethylpropyl]-6,14-*endo* -ethano-6,7,8,14-tetrahydrooripavine hydrochloride.. Buprenorphine hydrochloride has the molecular formula C<sub>29</sub> H<sub>41</sub> NO<sub>4</sub> HCl and the molecular weight is 504.09. The CAS number is 53152-21-9.

Naloxone hydrochloride is a white to slightly off-white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali. Chemically, it is (-)-17-Allyl-4,5 $\alpha$ -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. Naloxone hydrochloride has the molecular formula C<sub>19</sub> H<sub>21</sub> NO<sub>4</sub> HCl .2H<sub>2</sub> O and the molecular weight is 399.87. The CAS number of naloxone hydrochloride dihydrate is 51481-60-8.

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



buprenorphine hydrochloride



.HCl. 2H<sub>2</sub>O

naloxone hydrochloride dihydrate

### PHARMACOLOGY

#### *Pharmacodynamic properties*

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

During clinical pharmacology studies in opiate-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  $\mu$  (mu) 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 opiate dependent persons, the presence of

naloxone in SUBOXONE produces marked opiate antagonist effects and opiate withdrawal, thereby deterring intravenous abuse.

**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 1). 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. Naloxone did not appear to affect the pharmacokinetics of buprenorphine. SUBOXONE tablets are expected to deliver similar plasma concentrations of buprenorphine as tablets containing buprenorphine alone, with sublingual dosing.

Table 1.	Mean C <sub>max</sub> 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)
<b>Buprenorphine</b>				
Subjects	22	22	21	12
C <sub>max</sub> 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 <sub>0-t<sub>n</sub></sub> 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)
<b>Naloxone</b>				
Subjects	20	21	20	12
C <sub>max</sub> 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 drug 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 PRECAUTIONS and Interactions with Other Drugs) 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  $\mu$  (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.

**Elderly:** No pharmacokinetic data in elderly patients are available

### **CLINICAL TRIALS**

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

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-addicted 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 ( $p < 0.0001$ ).

## INDICATIONS

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

## 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 B or C)

Acute intoxication with alcohol or other CNS depressant.

Pregnant Women

Breast-feeding.

## PRECAUTIONS

*General:* SUBOXONE should be administered with caution in elderly or debilitated patients and those with impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (eg Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

Buprenorphine increases intracholedochal pressure as do other opiates. 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 and urethral stenosis.

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

***Respiratory Depression:*** 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 addicts have intravenously misused tablets containing buprenorphine as the only active, usually with benzodiazepines concomitantly. 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, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, 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.

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

***CNS Depression:*** Patients receiving SUBOXONE in the presence of other narcotic analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquillisers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. SUBOXONE should be used cautiously with MAOIs, based on experience with morphine.

**Hepatitis, Hepatic Events:** Hepatic necrosis and hepatitis with jaundice have been reported with buprenorphine use. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. 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, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues) could promote the occurrence of such hepatic injuries. These co-factors must be taken into account before prescribing SUBOXONE and during treatment monitoring. Measurements of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. If the drug treatment is continued, hepatic function should be monitored closely.

**Hepatic Disease:** Because buprenorphine is metabolised by the liver, its activity may be increased and/or extended in those individuals with impaired hepatic function. Naloxone metabolism may also be impaired in hepatic failure patients. Because hepatic elimination plays a relatively large role (~70%) in the overall clearance of SUBOXONE, lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.

**CYP3A4 Inhibitors:** Because CYP3A4 inhibitors may increase concentrations of buprenorphine, patients already treated with CYP3A4 inhibitors should have their dose of SUBOXONE titrated carefully since a reduced dose may be required in these patients (see **Interactions with Other Drugs**).

**Renal Disease:** Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine. Therefore no dose modification based on renal function is 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).

**Use in Ambulatory Patients:** SUBOXONE may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned accordingly. Like other opiates, SUBOXONE may produce orthostatic hypotension in ambulatory patients.

**Head Injury and Increased Intracranial Pressure:** SUBOXONE, like other potent opiates 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. SUBOXONE can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

**Opiate Withdrawal Effects:** Because SUBOXONE contains naloxone, it is highly likely to produce marked and intense opiate withdrawal symptoms if injected.

SUBOXONE may produce withdrawal symptoms in opiate dependent subjects if it is administered too soon after another opiate. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed. Studies in animals, as well as clinical experience, have showed that buprenorphine may produce dependence but at a lower level than morphine. Consequently, it is important to follow the **DOSAGE AND ADMINISTRATION** recommendations.

**Neonatal Abstinence Syndrome:** Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. Time to onset of withdrawal symptoms ranged from Day 1 to Day 8 of life with most (69%) occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in one case, apnoea and bradycardia were also reported. In many cases the withdrawal was serious and required treatment (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 or naloxone is a contraindication to SUBOXONE use.

### **Carcinogenicity & Mutagenicity**

#### **Carcinogenicity:**

In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100mg/kg/day, which equates to ca 14-fold human exposure at the maximum recommended clinical dose of 32mg 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 55mg/Kg/day (16 fold the maximal recommended human sublingual dose of 32mg, on a mg/m<sup>2</sup> basis); the no-effect dose was 5.4mg/Kg/day (twice the maximal human dose, on a mg/m<sup>2</sup> 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 6-115mg/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.

### **Impairment of 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 32mg/day (based on mg/m<sup>2</sup>). Dietary administration of Suboxone to rats at doses of 47mg/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 9.4mg/kg/day (twice the anticipated clinical exposure for both buprenorphine (based on AUC) and naloxone (based on mg/m<sup>2</sup>) had no adverse effect on fertility.

### **Use In Pregnancy (Category C)**

In rats, oral administration of buprenorphine at doses up to 20 times the maximum clinical dose of 32mg/day (based on mg/m<sup>2</sup>) 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<sup>2</sup>) 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).

There are no adequate or well controlled studies of SUBOXONE 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. SUBOXONE is contraindicated in pregnancy (see **CONTRAINDICATIONS**). Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

### **Use In Lactation**

Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m<sup>2</sup>) 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<sup>2</sup>. Because buprenorphine is excreted into human milk, SUBOXONE should not be used in breast-feeding women.

### **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.

### Interactions with Other Drugs

A number of deaths and cases of coma have occurred when addicts have intravenously misused buprenorphine and benzodiazepines concomitantly. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBOXONE (see **PRECAUTIONS**).

**CYP3A4 inhibitors:** An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C<sub>max</sub> 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 (see **PRECAUTIONS**).

**CYP3A4 inducers:** The interaction of buprenorphine with CYP3A4 inducers has not been investigated; therefore it is recommended that patients receiving SUBOXONE should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

### Effects on Laboratory Tests

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

### ADVERSE REACTIONS

Adverse events reported to occur by at least 1% of patients being treated in clinical trials of SUBOXONE (CR96/013 + CR96/014) are shown in Table 2.

<b>Table 2</b>	<b>Very Common Adverse Events reported by at least 10% Of subjects</b>
Body as a whole	Headache, withdrawal syndrome
Digestive System	Constipation, nausea
Nervous System	Insomnia
Skin and Appendages	Sweating
<b>Common Adverse Events reported by at least 1% of subjects</b>	
Body as a whole	Asthenia, chills, fever, flu syndrome, infection, malaise, abdominal pain, back pain, chest pain, pain, accidental injury
Cardiovascular System	Migraine, hypertension, vasodilation.
Digestive System	Anorexia, diarrhoea, nausea/vomiting, vomiting, dyspepsia, liver function abnormal, flatulence.
Metabolic/Nutritional Disorders	Peripheral oedema, weight decreased
Musculoskeletal System	Arthralgia, leg cramps, myalgia-
Nervous System	Anxiety, depression, dizziness, hypertonia, nervousness, paresthesia, somnolence, thinking abnormal, libido decreased.
Respiratory System	Cough increased, pharyngitis, rhinitis.
Skin and Appendages	Rash, pruritus, urticaria
Special Senses	Lacrimation disorder, amblyopia
Urogenital System	Impotence, urine abnormality

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

As with other opiates, orthostatic hypotension can occur (see **PRECAUTIONS**).

### **Post-marketing experience with buprenorphine alone**

Post-marketing experience with buprenorphine alone for treatment of opiate dependency has been associated with the following rare side effects: respiratory depression and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, foetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, and deaths.

Additionally, post-marketing experience with SUBOXONE for treatment of opiate dependency has been associated rarely with the following side effects: insomnia, reduced feeling, anorexia (see also Table 2 above), amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath, and suicide ideation.

Cases of hepatitis with jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and asymptomatic elevations in hepatic transaminases have been reported with buprenorphine use (see **PRECAUTIONS**).

In cases of intravenous misuse of buprenorphine, local reactions, sometimes septic, and potentially serious acute hepatitis 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 **PRECAUTIONS** and **CONTRAINDICATIONS**).

### **DOSAGE AND ADMINISTRATION**

Treatment with SUBOXONE sublingual tablets is intended for adults and children aged 16 years or over who have agreed to be treated for addiction. When initiating SUBOXONE treatment, the physician should be aware that it can precipitate withdrawal in opioid-dependent patients if given too soon after the administration of heroin, methadone or another opiate.

The route of administration of SUBOXONE is sublingual. 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 drug.

**Please note:** The following instructions refer to the buprenorphine content of each dose. SUBOXONE 8mg/2mg (buprenorphine/naloxone) is referred to as the 8mg dose and SUBOXONE 2mg/0.5mg (buprenorphine/naloxone) is referred to as the 2mg dose.

#### **Method of Administration**

Suboxone tablets are to be placed under the tongue until dissolved, which usually requires 2 to 10 minutes. 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 opiate withdrawal symptoms due to inadequate dosage.

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

**Patients taking Street Heroin (or Other Short-acting Opiates):** When treatment starts the dose of SUBOXONE should be taken at least 6 hours after the patient last used opiates or when the early signs of withdrawal appear. The recommended starting dose is 4 mg SUBOXONE on Day One, with a possible additional 4 mg depending on the individual patient's requirement.

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

**Dosage Adjustment and Maintenance**

The dose of SUBOXONE 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.

**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 8mg may be given 16mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 32mg.

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 32mg.

**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 3.

<b>Table 3. Gradual dose taper schedule</b>			
<b>Week</b>	<b>20mg Maintenance dose</b>	<b>16mg Maintenance dose</b>	<b>8mg Maintenance dose</b>
1	16mg	12mg	8mg
2	8mg	8mg	4mg
3	4mg	4mg	4mg

**OVERDOSAGE**

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

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. 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.

**PRESENTATION**

SUBOXONE is supplied as white, hexagonal sublingual tablets containing 2mg buprenorphine + 0.5mg naloxone and 8mg buprenorphine + 2mg naloxone. The tablets are packed in aluminium / aluminium blister strips of 7 tablets in pack sizes of 28 tablets.

Store below 30°C.

**CLASSIFICATION**

Controlled Drug: C4

**NAME AND ADDRESS OF SPONSOR**

Reckitt Benckiser  
289 Lincoln Road  
Henderson  
Auckland

**DATE OF PREPARATION: 21 March 2006**