1. NAME OF THE MEDICINAL PRODUCT

SUBOXONE® Sublingual Tablet

2MG/0.5MG & 8MG/2MG

SUBOXONE sublingual tablets contain buprenorphine (as hydrochloride) and naloxone (as hydrochloride dihydrate) at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SUBOXONE 2 mg/0.5 mg sublingual tablet contains 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate).

Each SUBOXONE 8 mg/2 mg sublingual tablet contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate).

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

SUBOXONE 2mg/0.5mg sublingual tablets are white, hexagonal, biconvex, and debossed with “N2”.

SUBOXONE 8mg/2mg sublingual tablets are white, hexagonal, biconvex, and debossed with “N8”.

The sublingual formulation is not designed to be split or broken.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

4.2 Posology and method of administration

Administration is sublingual.

Treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction.

Each SUBOXONE sublingual tablet contains buprenorphine and naloxone.

Method of administration

Physicians must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

SUBOXONE sublingual tablets are to be placed under the tongue until dissolved, which usually requires 5 to 10 minutes. Patients should not swallow or consume food or drink until the tablet is completely dissolved. The dose is made up from SUBOXONE 2 mg/0.5 mg and SUBOXONE 8 mg/2 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.

Posology

Precautions to be taken before induction

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 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

To avoid precipitating withdrawal, induction with SUBOXONE or buprenorphine only tablets should be undertaken when objective signs of withdrawal appear.

Initiation therapy
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. The Clinical Opiate Withdrawal Scale (COWS) may be a useful reference assessment however clinical assessment of withdrawal symptoms with consideration of the patient's baseline presentation is important, particularly for patients in mild withdrawal (COWS score of 5-12). The recommended starting dose is 4-8 mg SUBOXONE 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. For patients with moderate or severe withdrawal at the time of the first dose, an initial dose of 8 mg may be appropriate with an additional 4 mg depending on the individual patient's requirement to a total maximum of 12 mg on Day 1.

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

Patients on Methadone
Before starting treatment with SUBOXONE, the maintenance dose of methadone should be reduced to a 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. An initial dose of 2 mg SUBOXONE may be administered when moderate withdrawal is apparent (COWS ≥ 13). An additional dose of 6 mg SUBOXONE can be administered one hour later if the initial dose does not precipitate withdrawal. Supplementary doses can be administered every 1 to 3 hours according to withdrawal severity:

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

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

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

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.

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

During the initiation of treatment, daily dispensing of buprenorphine is recommended. After stabilisation, a reliable patient may be given a supply of SUBOXONE sufficient for several days of treatment. It is recommended that the amount of SUBOXONE be limited to 7 days according to local requirements.

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 SUBOXONE 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.

Dosage reduction and termination of treatment
After a satisfactory stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of the sublingual tablet in doses of 2 mg and 8 mg allows for a downward titration of dosage. Patients should be monitored following termination of treatment because of the potential for relapse.

Older People
The safety and efficacy of SUBOXONE in elderly patients over 65 years of age have not been established. No recommendation on posology can be made.

Paediatrics
SUBOXONE is not recommended for use in children below age 15 years due to lack of data on safety and efficacy.

Hepatic impairment
Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicinal products (see INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended.

Both active substances of SUBOXONE, buprenorphine and naloxone, are extensively metabolised in the liver, and the plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine. As SUBOXONE pharmacokinetics may be altered in patients with hepatic impairment, lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended (see PHARMACOKINETIC PROPERTIES).

Patients with impaired renal function
Modification of the SUBOXONE dose is not generally required in patients with renal insufficiency. Caution is recommended when dosing patients with severe renal impairment (< 30 ml/min) (see PHARMACOKINETIC PROPERTIES).

4.3 Contraindications
SUBOXONE is contraindicated in the following instances:
- Hypersensitivity to buprenorphine, to naloxone, or to any other component of the tablet,
- 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.

Misuse, abuse and diversion
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 or diversion, appropriate precautions should be taken when prescribing and dispensing SUBOXONE, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

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

Combining buprenorphine with naloxone in SUBOXONE is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of SUBOXONE is expected to be less likely than buprenorphine alone since the naloxone in SUBOXONE can precipitate withdrawal in individuals dependent on heroin, methadone, or other opioid agonists.

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 buprenorphine was used in combination with benzodiazepines (see INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION), 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. If buprenorphine is administered to some non-opioid dependent individuals, who are not tolerant to the effects of opioids, potentially fatal respiratory depression may occur.

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 (curvature of spine leading to potential shortness of breath).

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

SUBOXONE may cause severe, possibly fatal, respiratory depression in children and non-dependent persons in case of accidental or deliberate ingestion. Patients must be warned to store the blister safely, to never open the blister in advance, to keep them out of the reach of children and other household members, and not to take this medicine in front of children. An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

CNS depression

SUBOXONE may cause drowsiness, particularly when used together with alcohol or central nervous system depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics) (see INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

Risks from Concomitant Use with Benzodiazepines

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of SUBOXONE with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when SUBOXONE is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

Dependence

Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience, have shown that buprenorphine may produce dependence, but at a lower level than a full agonist, e.g. morphine.

Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

Hepatitis and hepatic events

Cases of acute hepatic injury have been reported in opioid-dependent patients both in clinical trials and in 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, liver enzyme abnormalities, viral infections particularly chronic hepatitis C, 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 medicinal products and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended. These co-factors must be taken into account before prescribing SUBOXONE and during treatment monitoring.

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 the treatment is continued, hepatic function should be monitored closely.

Precipitation of opioid withdrawal syndrome

When initiating treatment with SUBOXONE, the physician must be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients particularly if administered less than 6 hours after the last use of heroin or other short acting opioid, or if administered less than 24 hours after the last dose of methadone (see POSOLOGY AND METHOD OF ADMINISTRATION). Patients should be clearly monitored during the switching period from buprenorphine or methadone to SUBOXONE since withdrawal symptoms

have been reported. To avoid precipitating withdrawal upon induction from short-acting or long-acting opioids, the patient should show objective signs and symptoms of moderate withdrawal prior to induction dosing.

Withdrawal symptoms may also be associated with suboptimal dosing.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study, in which a SUBOXONE 2 mg/0.5 mg sublingual tablet was administered to healthy subjects and subjects with varying degrees of hepatic impairment. Since both buprenorphine and naloxone are extensively metabolised, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment which may require dose adjustments. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine. SUBOXONE sublingual tablets should be used with caution in patients with moderate to severe hepatic impairment (See section PHARMACOKINETIC PROPERTIES).

Table 1 summarises the results from a clinical trial in which the exposure after single-dose administration of SUBOXONE 2 mg/0.5 mg (buprenorphine/naloxone) sublingual tablet was determined in healthy subjects, and in subjects with hepatic impairment.

Table 1. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following SUBOXONE sublingual tablet administration (change relative to healthy subjects)

PK Parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
Buprenorphine			
C_{max}	1.2-fold increase	1.1-fold increase	1.7-fold increase
AUC_{last}	Similar to control	1.6-fold increase	2.8-fold increase
Naloxone			
C_{max}	Similar to control	2.7-fold increase	11.3-fold increase
AUC_{last}	0.2-fold decrease	3.2-fold increase	14.0-fold increase

Overall, buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function, while naloxone plasma exposure increased 14-fold with severely impaired hepatic function.

Renal impairment

Renal elimination plays a relatively small role 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 (creatinine clearance <30 ml/min) (see PHARMACOKINETIC PROPERTIES POSOLOGY AND METHOD OF ADMINISTRATION).

Use in adolescents (Age ≤18)

Due to the limited amount of available data, patients below the age of 18 should be more closely monitored during treatment.

CYP3A4 inhibitors
Medicines that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the SUBOXONE dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of SUBOXONE titrated carefully since a reduced dose may be sufficient in these patients (see INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

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.

General warnings relevant to the administration of opioids
Opioids may produce orthostatic hypotension in ambulatory patients.

Opioids may elevate cerebrospinal fluid pressure, which may cause seizures, and should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.

Opioids should be used with caution in patients with hypotension, prostatic hypertrophy or urethral stenosis.

Opioid-induced miosis, 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.

Opioids should be used with caution in patients with myxoedema, hypothyroidism, or adrenal cortical insufficiency (e.g. Addison's disease).

Opioids have been shown to increase intracholedochal pressure and should be used with caution in patients with dysfunction of the biliary tract.

Opioids should be administered with caution to elderly or debilitated patients.

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of SUBOXONE with serotonergic drugs (See INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION). The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later than that. Discontinue SUBOXONE if serotonin syndrome is suspected.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with

physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Sexual Function/Reproduction

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Post marketing experience).

4.5 Interaction with other medicinal products and other forms of interaction

SUBOXONE should not be taken together with:

- Alcoholic drinks or medications containing alcohol, as alcohol increases the sedative effect of buprenorphine (see EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

SUBOXONE should be used cautiously when co-administered with:

- 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 directed by their physician (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
  Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
  The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
  Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
  Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.
- Other central nervous system depressants, other opioid derivatives (e.g. methadone, analgesics and antitussives), certain antidepressants, sedative H1- receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: these combinations increase central nervous system depressant effects. The reduced level of alertness can make driving and using machines hazardous.
- Serotonergic Drugs: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue SUBOXONE if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See 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 to overdose with a full agonist exists, 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 dependent treatment specialists.

- Naltrexone is an opioid antagonist that can block the pharmacological effects of buprenorphine. Co-administration during SUBOXONE treatment should be strongly avoided, due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms.
- CYP3A4 inhibitors: an interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC (area under the curve) 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 or azole antifungals like ketoconazole or itraconazole).
- CYP3A4 inducers: Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in sub-optimal treatment of opioid dependence with buprenorphine. It is recommended that patients receiving SUBOXONE should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin and rifampicin) are co-administered. The dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

4.6 Pregnancy, Lactation and Fertility

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).

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, apnoea, bradycardia, myoclonus or convulsions). In many reported cases the withdrawal was serious and required treatment. 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.

Furthermore, the use of SUBOXONE during pregnancy should be assessed by the physician. SUBOXONE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

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

Lactation
Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response). The no effect level for developmental effects was twice the maximum clinical dose, based on mg/m^2. In two studies of thirteen women, buprenorphine was found in low levels in human breast milk. In both studies the estimated infant dose was <1% of the maternal dose. Because buprenorphine is excreted into human milk, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBOXONE 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
In general, SUBOXONE may influence the ability to move safely in traffic, use machines, or perform other hazardous activities when administered to opioid dependent patients. SUBOXONE may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used together with alcohol or other central nervous system depressants, the effect is likely to be more pronounced. Therefore, caution is advised when performing the above mentioned activities until they are reasonably certain that SUBOXONE therapy does not adversely affect their ability to engage in such activities (see INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION and SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.8 Undesirable effects
Summary of the safety profile
The most common treatment related undesirable effects reported during clinical studies with SUBOXONE were those related to withdrawal symptoms (i.e. insomnia, headache, nausea, hyperhidrosis and pain). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

Tabulated list of adverse reactions
Table 2 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 2: Treatment-related adverse reactions reported in clinical studies of SUBOXONE

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 Leukocytosis Leukopenia Lymphadenopathy Thrombocytopenia
Immune system disorders		
		Hypersensitivity
Metabolism and nutrition disorders		
	Decreased appetite	Hyperglycaemia Hyperlipidaemia Hypoglycaemia
Psychiatric disorders		
Insomnia	Anxiety Depression Libido decreased Nervousness Thinking abnormal	Abnormal dreams Agitation Apathy Depersonalisation Drug dependence Euphoric mood Hostility
Nervous system disorders		
Headache	Migraine Dizziness Hypertonia Paraesthesia Somnolence	Amnesia Convulsion Hyperkinesia Speech disorder Tremor
Eye disorders		
	Amblyopia Lacrimal disorder	Conjunctivitis Miosis
Cardiac disorders		
		Angina pectoris Bradycardia Myocardial infarction Palpitations Tachycardia
Vascular disorders		
	Hypertension Vasodilatation	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Cough	Asthma Dyspnoea Yawning

Gastrointestinal disorders		
Constipation Nausea	Abdominal Pain Diarrhoea Dyspepsia Flatulence Vomiting	Mouth ulceration Tongue discolouration
Skin and subcutaneous tissue disorders		
Hyperhidrosis	Pruritus Rash Urticaria	Acne Alopecia Dermatitis exfoliative Dry skin Skin mass
Musculoskeletal and connective tissue disorders		
	Back Pain Arthralgia Muscle spasms Myalgia Leg cramps	Arthritis
Renal and urinary disorders		
	Urine Abnormality	Albuminuria Dysuria Haematuria Nephrolithiasis Urinary retention
Reproductive system and breast disorders		
	Erectile dysfunction	Amenorrhoea Ejaculation disorder Menorrhagia Metrorrhagia
General disorders and administration site conditions		
Drug withdrawal syndrome	Asthenia Chest Pain Chills Pyrexia Malaise Pain Oedema peripheral Injury	Hypothermia Heat stroke
Investigations		
	Liver function test abnormal Weight decreased	Blood creatinine increased

Post marketing experience

The most common adverse drug reactions reported during post-marketing surveillance are captured in Table 3. Events occurring in at least 1% of reports by 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 3: 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.

Description of other selected adverse reactions observed post-marketing

The following is a summary of other post-marketing adverse event reports that are considered serious or otherwise noteworthy, some of which may have only been observed with buprenorphine alone in the treatment of opioid dependence:

- In cases of intravenous misuse, local reactions, sometimes septic (abscess, cellulitis), and potentially serious acute hepatitis and other acute infections such as pneumonia, endocarditis have been reported (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- The most common signs and symptoms of hypersensitivity include rashes, urticaria, and pruritus. Cases of bronchospasm, respiratory depression, angioedema, and anaphylactic shock have been reported (see section CONTRAINDICATION).
- Hepatic transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and hepatic necrosis have occurred (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Hallucination, orthostatic hypotension, syncope and vertigo have been reported. In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.
- A neonatal abstinence syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see FERTILITY, PREGNANCY AND LACTATION).

Serotonin syndrome (See SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Adrenal insufficiency (See SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may

influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the local reporting system.

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

Treatment
In the event of 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.

Symptomatic treatment of respiratory depression, and standard intensive care measures, should be implemented. A patent airway and institution of assisted or controlled ventilation must be assured. 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.

Use of an opioid antagonist (i.e. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.

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. If infusion is not possible, repeated dosing with naloxone may be required. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

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

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

Naloxone is an antagonist at μ (mu), δ (delta), and κ (kappa) opioid receptors. Because of its almost complete first pass metabolism, naloxone administered orally 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.

5.2 Pharmacokinetic properties

Table 4: Pharmacokinetic parameters (Mean ± SD) of buprenorphine, norbuprenorphine and naloxone following SUBOXONE sublingual tablet administration

PK Parameter	SUBOXONE sublingual tablet Dose (mg)			
	2/0.5	8/2	12/3	16/4
Buprenorphine				
C_{max} (ng/ml)	0.780 ± 0.323	2.58 ± 1.10	4.60 ± 1.72	5.51 ± 2.18
T_{max} (hr)*	1.50 (0.75-3.00)	1.50 (0.50-3.03)	1.25 (0.75-3.00)	1.00 (0.50-2.00)
AUC_{inf} (ng.hr/ml)	7.651 ± 2.650	25.31 ± 9.500	43.9 ± 13.0	54.7 ± 20.9
$t_{1/2}$ (hr)	30.75 ± 15.04	31.94 ± 15.27	41.5 ± 10.4	39.6 ± 11.4
Norbuprenorphine				
C_{max} (ng/ml)	0.293 ± 0.129	1.35 ± 0.977	2.29 ± 1.09	2.75 ± 1.01
T_{max} (hr)*	1.25 (0.50-8.00)	1.25 (0.75-12.00)	1.25 (0.75-24.00)	1.00 (0.50-4.00)
AUC_{inf} (ng.hr/ml)	13.59 ± 4.887	52.84 ± 31.15	84.4 ± 32.2	97.2 ± 34.4
$t_{1/2}$ (hr)	45.84 ± 15.85	44.76 ± 28.74	48.5 ± 17.5	45.0 ± 16.6
Naloxone				
C_{max} (pg/ml)	51.3 ± 21.1	135 ± 57.3	162 ± 89.7	241 ± 114
T_{max} (hr)*	0.75 (0.30-1.50)	0.75 (0.50-1.25)	0.75 (0.25-2.00)	0.75 (0.25-1.50)
AUC_{inf} (pg · hr/ml)	124.2 ± 52.49	374.6 ± 132.8	417 ± 173	653 ± 271
$t_{1/2}$ (hr)	5.15 ± 5.28	7.65 ± 3.99	4.63 ± 5.43	5.60 ± 5.79

*T_{max} is reported as median value with range.

Absorption

Plasma levels of buprenorphine increased with increasing sublingual dose of SUBOXONE. There was wide inter-patient variability in buprenorphine plasma levels, but within subjects the variability was low.

Naloxone has not been found to affect the pharmacokinetics of buprenorphine and both buprenorphine sublingual tablets and SUBOXONE sublingual tablets deliver similar plasma concentrations of buprenorphine.

Distribution

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

Biotransformation

Buprenorphine is primarily metabolised through N-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation.

Norbuprenorphine binds to opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of SUBOXONE.

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

Elimination
Elimination of buprenorphine is bi- or tri-exponential, and buprenorphine has a long terminal elimination half-life from plasma (see Table 4).

Buprenorphine is eliminated in the faeces (~70%) by biliary excretion of the glucuroconjugated metabolites following intramuscular (IM) administration, the rest (~30%) being eliminated in the urine. Following sublingual administration to a single male subject, about 13% of a buprenorphine dose was recovered in the urine.

The elimination half-life from plasma for naloxone is reported in Table 4. Naloxone is excreted in the urine.

Clinical Efficacy
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. In this trial, 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 ($p < 0.0001$).

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution to a full agonist active control, 162 subjects were randomised to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of SUBOXONE), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to 10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually. Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control, in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of buprenorphine, 8 mg per day was similar to that of the moderate active control dose, but equivalence was not demonstrated.

5.3 Preclinical safety data
The combination of buprenorphine and naloxone has been investigated in acute and repeated dose (up to 90 days in rats) toxicity studies in animals. No synergistic enhancement of toxicity has been observed. Undesirable effects were based on the known pharmacological activity of opioid agonistic and/or antagonistic substances.

The combination (4:1) of buprenorphine hydrochloride and naloxone hydrochloride was not mutagenic in a bacterial mutation assay (Ames test) and was not clastogenic in an in vitro cytogenetic assay in human lymphocytes or in an intravenous micronucleus test in the rat.

A carcinogenicity study with SUBOXONE was conducted in rats at doses of 7, 30 and 120 mg/kg/day, with estimated exposure multiples of 3 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m^2 basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

An Environmental Risk Assessment of SUBOXONE concluded that the use of SUBOXONE is not expected to have an adverse impact on the environment.

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 flavor

6.4 Special precautions for storage

The shelf-life of SUBOXONE sublingual tablets is 3 years. Store below 30°C. No special storage precautions are required.

6.5 Nature and contents of container

Sublingual tablet in blister packs of 7 and 28 tablets.

Keep out of reach of children.

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7. PRODUCT REGISTRATION HOLDER

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