ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 2 mg/0.5 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Each sublingual tablet contains 42 mg lactose (as monohydrate)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

White hexagonal biconvex tablets of 6.5 mm with “N2” debossed on one side.

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

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

Precautions to be taken before induction
Prior to treatment initiation, 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 of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine/naloxone or buprenorphine only should be undertaken when objective and clear signs of withdrawal are evident (demonstrated e.g. by a score indicating mild to moderate withdrawal on the validated Clinical Opioid Withdrawal Scale, COWS).

- For patients dependent upon heroin or short-acting opioids, the first dose of buprenorphine/naloxone should be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.
- For patients receiving methadone, the dose of methadone should be reduced to a maximum of 30 mg/day before beginning buprenorphine/naloxone therapy. The long half life of methadone should be considered when starting buprenorphine/naloxone. The first dose of buprenorphine/naloxone should be taken only when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

Posology

Initiation therapy (induction)
The recommended starting dose in adults and adolescents over 15 years of age is one to two Suboxone 2 mg/0.5 mg. An additional one to two Suboxone 2 mg/0.5 mg may be administered on day one depending on the individual patient's requirement.
During the initiation of treatment, daily supervision of dosing 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 therapy
Following treatment induction on day one, the patient should be stabilised to a maintenance dose during the next few days by progressively adjusting the dose according to the clinical effect of the individual patient. Dose titration in steps of 2-8 mg buprenorphine is guided by reassessment of the clinical and psychological status of the patient, and should not exceed a maximum single daily dose of 24 mg buprenorphine.

Less than daily dosing
After a satisfactory 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 buprenorphine may be given 16 mg buprenorphine on alternate days, with no dose on the intervening days. In some patients, after a satisfactory 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 dose on the intervening days. However, the dose given on any one day should not exceed 24 mg buprenorphine. Patients requiring a titrated daily dose> 8 mg buprenorphine /day may not find this regimen adequate.

Medical withdrawal
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 doses of 2 mg/0.5 mg and 8 mg/2 mg allows for a downward titration of dosage. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg may be used. Patients should be monitored following medical withdrawal because of the potential for relapse.

Special populations

Elderly
The safety and efficacy of buprenorphine/naloxone in elderly patients over 65 years of age have not been established. No recommendation on posology can be made.

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 section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).
Both active substances of Suboxone, buprenorphine and naloxone, are extensively metabolized 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 buprenorphine/naloxone 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. Buprenorphine/naloxone is contraindicated in patients with severe hepatic impairment. (see section 4.3 and 5.2).

Renal impairment
Modification of the buprenorphine/naloxone dose is not required in patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4 and 5.2).

Paediatric population
The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established. No data are available.

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 section 4.4). The tablet is to be placed under the tongue until completely dissolved. Patients should not swallow or consume food or drink until the tablet is completely dissolved.

The dose is made up from multiple Suboxone tablets of different strengths, 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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Severe respiratory insufficiency
Severe hepatic impairment
Acute alcoholism or *delirium tremens*.
Concomitant administration of opioid antagonists (naltrexone, nalmefene) for the treatment of alcohol or opioid dependence.

4.4 Special warnings and precautions for use

Misuse, abuse and diversion
Buprenorphine 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 or localised and systemic infections, respiratory depression and hepatic injury. Buprenorphine misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicinal product is not safeguarded against theft.

Sub-optimal treatment with buprenorphine/naloxone may prompt medicine misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine/naloxone may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

To minimize the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, 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 needs.

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
A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines (see section 4.5) or when buprenorphine was not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and 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.

This product should be used with care in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath)).

Buprenorphine/naloxone 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
Buprenorphine/naloxone may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants (such as tranquilisers, sedatives or hypnotics) (see section 4.5).

Dependence
Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience, have demonstrated 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 addicts 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 hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines) and ongoing injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing buprenorphine/naloxone and during treatment. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.

Precipitation of opioid withdrawal syndrome
When initiating treatment with buprenorphine/naloxone, 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. Patients should be clearly monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported. To avoid precipitating withdrawal, induction with buprenorphine/naloxone should be undertaken when objective signs of withdrawal are evident (see section 4.2).

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

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Since both buprenorphine and naloxone are extensively metabolized, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment after single-dose administration. 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 hepatic impairment (See section 4.3 and 5.2). In patients with severe hepatic insufficiency the use of buprenorphine/naloxone is contraindicated.

Renal impairment
Renal elimination may be prolonged since 30 % of the administered dose is eliminated by the renal route. 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 sections 4.2 and 5.2).

Use in adolescents (Age 15-<18)
Due to the lack of data in adolescents (age 15-<18), patients in this age group should be more closely monitored during treatment.

CYP 3A inhibitors
Medicines that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the buprenorphine/naloxone dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of buprenorphine/naloxone titrated carefully since a reduced dose may be sufficient in these patients (see section 4.5).

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, so opioids 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.

The concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine (see section 4.5).

Suboxone contains lactose. Patients with rare hereditary problems of galactose intolerance, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Suboxone should not be taken together with:

- alcoholic drinks or medicines containing alcohol, as alcohol increases the sedative effect of buprenorphine (see section 4.7).

Suboxone should be used cautiously when co-administered with:

- benzodiazepines: This combination may result in death due to respiratory depression of central origin. Therefore, dosages must be limited and this combination must 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 section 4.4).

- other central nervous system depressants, other opioid derivatives (e.g. methadone, analgesics and antitussives), certain antidepressants, sedative H_1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: these combinations increase central nervous system depression. The reduced level of alertness can make driving and using machines hazardous.

- Furthermore, adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine/naloxone. Therefore 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.

- naltrexone and nalmefene are opioid antagonists that can block the pharmacological effects of buprenorphine. Co-administration during buprenorphine/naloxone treatment is contraindicated due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms (see section 4.3).

- 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 such as ketoconazole or itraconazole, macrolide antibiotics).

- 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 buprenorphine/naloxone should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. The dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

- the concomitant use of monoamine oxidase inhibitors (MAOI) might produce exaggeration of the effects of opioids, based on experience with morphine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Suboxone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Towards the end of pregnancy buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate (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.

Furthermore, the use of buprenorphine/naloxone during pregnancy should be assessed by the physician. Buprenorphine/naloxone should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
It is unknown whether naloxone is excreted in human breast milk. Buprenorphine and its metabolites are excreted in human breast milk. In rats buprenorphine has been found to inhibit lactation. Therefore, breastfeeding should be discontinued during treatment with Suboxone.

Fertility
Animal studies have shown a reduction in female fertility at high doses (systemic exposure > 2.4 times the human exposure at the maximum recommended dose of 24 mg buprenorphine, based on AUC). See section 5.3.

4.7 Effects on ability to drive and use machines

Buprenorphine/naloxone has minor to moderate influence on the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If taken together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see sections 4.4 and 4.5).

Patients should be cautioned about driving or operating hazardous machinery in case buprenorphine/naloxone may affect their ability to engage in such activities.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported treatment related adverse reactions reported during the pivotal clinical trials were constipation and symptoms commonly associated with drug withdrawal (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 1 summarises adverse reactions reported from pivotal clinical trials in which, 342 of 472 patients (72.5 %) reported adverse reactions and adverse reactions reported during post-marketing surveillance.

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), Not known (cannot be estimated from available data).

Table 1: Treatment-related adverse reactions reported in clinical trials and post-marketing surveillance of buprenorphine/naloxone

System Organ Class	**Very common**	**Common**	**Uncommon**	**Not Known**
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	Anaphylactic shock
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	Hallucination
Nervous system disorders	Headache	Migraine Dizziness Hypertonia Paraesthesia Somnolence	Amnesia Hyperkinesia Seizure Speech disorder Tremor	Hepatic encephalopathy Syncope
Eye disorders		Amblyopia Lacrimal disorder	Conjunctivitis Miosis	
Ear and labyrinth disorders				Vertigo
Cardiac disorders			Angina Pectoris Bradycardia Myocardial infarction Palpitations Tachycardia	
Vascular disorders		Hypertension Vasodilatation	Hypotension	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		Cough	Asthma Dyspnoea Yawning	Bronchospasm Respiratory depression
Gastrointestinal	Constipation	Abdominal Pain	Mouth ulceration	

disorders	Nausea	Diarrhoea Dyspepsia Flatulence Vomiting	Tongue discolouration	
Hepatobiliary disorders				Hepatitis Hepatitis acute Jaundice Hepatic necrosis Hepatorenal syndrome
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pruritus Rash Urticaria	Acne Alopecia Dermatitis exfoliative Dry skin Skin mass	Angioedema
Musculoskeletal and connective tissue disorders		Back Pain Arthralgia Muscle spasms Myalgia	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	Hypothermia	Drug withdrawal syndrome neonatal (see section 4.6)
Investigations		Liver function test abnormal Weight decreased	Blood creatinine increased	Transaminases increased
Injury, poisoning and procedural complications		Injury	Heat stroke	

Description of selected adverse reactions

In cases of intravenous drug misuse, some adverse experiences are attributed to the act of misuse rather than the medicinal product and include local reactions, sometimes septic (abscess, cellulitis), and potentially serious acute hepatitis, and other acute infections such as pneumonia, endocarditis have been reported (see section 4.4).

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a drug withdrawal syndrome similar to that associated with naloxone (see sections 4.2 and 4.4).

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Respiratory depression as a result of central nervous system depression is the primary symptom requiring intervention in the case of overdose because it may lead to respiratory arrest and death. Signs of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and/or speech disorders.

Management
General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, and standard intensive care measures, should be implemented. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

If the patient vomits, care must be taken to prevent aspiration of the vomitus.

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.

If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance 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. Initial naloxone doses may range up to 2 mg and be repeated every 2-3 minutes until a satisfactory response is achieved, but should not exceed a 10 mg starting dose. Ongoing intravenous infusion rates should be titrated to patient response.

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 an opioid partial agonist/antagonist which binds to the μ and κ (kappa) opioid receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the μ-opioid receptors which, over a prolonged period, might minimise the need of addicted patients for drugs.

Opioid agonist ceiling effects were observed during clinical pharmacology studies in opioid-dependent persons.

Naloxone is an antagonist at μ-opioid receptors. When administered orally or sublingually in usual doses to patients experiencing opioid withdrawal, naloxone exhibits little or no pharmacological effect because of its almost complete first pass metabolism. 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 efficacy

Efficacy and safety data for buprenorphine/naloxone are primarily derived from a one-year clinical trial, comprising a 4-week randomised double blind comparison of buprenorphine/naloxone, buprenorphine and placebo followed by a 48 week safety study of buprenorphine/naloxone. In this trial, 326 heroin-addicted subjects were randomly assigned to either buprenorphine/naloxone 16 mg per day, 16 mg buprenorphine per day or placebo. For subjects randomized to either active treatment, dosing began with 8 mg of buprenorphine on Day 1, followed by 16 mg (two 8 mg) of buprenorphine on Day 2. On Day 3, those randomized to receive buprenorphine/naloxone 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 buprenorphine/naloxone individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both buprenorphine/naloxone 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 randomized 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 buprenorphine/naloxone), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to10 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.

5.2 Pharmacokinetic properties

Buprenorphine

Absorption

Buprenorphine, when taken orally, undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of this medicinal product by the oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration. Plasma levels of buprenorphine increased with the sublingual dose of buprenorphine/naloxone. Both C_{max} and AUC of buprenorphine increased with the increase in dose (in the range of 4-16 mg), although the increase was less than dose-proportional.

Pharmacokinetic Parameter	**Suboxone 4 mg**	**Suboxone 8 mg**	**Suboxone 16 mg**
C_{max} ng/ml	1.84 (39)	3.0 (51)	5.95 (38)
AUC_{0-48} hour ng/ml	12.52 (35)	20.22 (43)	34.89 (33)

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

Biotransformation and elimination
Buprenorphine is metabolised by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirm that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N-dealkylbuprenorphine is a μ-opioid agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri-exponential, and has a mean half-life from plasma of 32 hours.
Buprenorphine is eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70 %), the rest being eliminated in the urine.

Naloxone

Absorption and distribution
Following intravenous administration, naloxone is rapidly distributed (distribution half-life ~ 4 minutes). Following oral administration, naloxone is barely detectable in plasma; following sublingual administration of buprenorphine/naloxone, plasma naloxone concentrations are low and decline rapidly.

Biotransformation
The medicinal product is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone has a mean half-life from plasma of 1.2 hours.

Special populations

Elderly
No pharmacokinetic data in elderly patients are available.

Renal impairment
Renal elimination plays a relatively small role (~30 %) in the overall clearance of buprenorphine/naloxone. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment (see Section 4.3).

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study.

Table 3 summarizes the results from a clinical trial in which the exposure after single-dose administration of Suboxone 2.0/0.5mg (buprenorphine/naloxone) sublingual tablet was determined in healthy subjects, and in subjects with hepatic impairment.

Table 3. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following SUBOXONE 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.

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.

Reproduction studies by oral administration of buprenorphine: naloxone (ratio 1:1) indicated that embryolethality occurred in rats in the presence of maternal toxicity at all doses. The lowest dose studied represented exposure multiples of 1x for buprenorphine and 5x for naloxone at the maximum human therapeutic dose calculated on a mg/m² basis. No developmental toxicity was observed in rabbits at maternally toxic doses. Further, no teratogenicity has been observed in either rats or rabbits. A peri-postnatal study has not been conducted with buprenorphine/naloxone; however, maternal oral administration of buprenorphine at high doses during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm

(estimated exposure approximately 2.4x for buprenorphine at a human dose of 24 mg buprenorphine/naloxone based on AUC, plasma levels of naloxone were below the limit of detection in rats) had no adverse effect on fertility in females.

A carcinogenicity study with buprenorphine/naloxone 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/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol
Maize starch
Povidone K 30
Citric acid anhydrous
Sodium citrate
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

This medicinal product does not require any special storage conditions.

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.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Indivior UK Limited
103 – 105 Bath Road
Slough
Berkshire
SL1 3UH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/001
EU/1/06/359/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 26 September 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 8 mg/2 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Each sublingual tablet contains 168 mg lactose (as monohydrate)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

White hexagonal biconvex tablets of 11 mm with “N8” debossed on one side.

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

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

Precautions to be taken before induction

Prior to treatment initiation, 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 of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine/naloxone or buprenorphine only should be undertaken when objective and clear signs of withdrawal are evident (demonstrated e.g. by a score indicating mild to moderate withdrawal on the validated Clinical Opioid Withdrawal Scale, COWS).

- For patients dependent upon heroin or short-acting opioids, the first dose of buprenorphine/naloxone should be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.
- For patients receiving methadone, the dose of methadone should be reduced to a maximum of 30 mg/day before beginning buprenorphine/naloxone therapy. The long half life of methadone should be considered when starting buprenorphine/naloxone. The first dose of buprenorphine/naloxone should be taken only when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

Posology

Initiation therapy (induction)
The recommended starting dose in adults and adolescents over 15 years of age is one to two Suboxone 2 mg/0.5 mg. An additional one to two Suboxone 2 mg/0.5 mg may be administered on day one depending on the individual patient's requirement.
During the initiation of treatment, daily supervision of dosing 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 therapy
Following treatment induction on day one, the patient should be stabilised to a maintenance dose during the next few days by progressively adjusting the dose according to the clinical effect of the individual patient. Dose titration in steps of 2-8 mg buprenorphine is guided by reassessment of the clinical and psychological status of the patient, and should not exceed a maximum single daily dose of 24 mg buprenorphine.

Less than daily dosing
After a satisfactory 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 buprenorphine may be given 16 mg buprenorphine on alternate days, with no dose on the intervening days. In some patients, after a satisfactory 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 dose on the intervening days. However, the dose given on any one day should not exceed 24 mg buprenorphine. Patients requiring a titrated daily dose> 8 mg buprenorphine /day may not find this regimen adequate.

Medical withdrawal
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 doses of 2 mg/0.5 mg and 8 mg/2 mg allows for a downward titration of dosage. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg may be used. Patients should be monitored following medical withdrawal because of the potential for relapse.

Special populations

Elderly
The safety and efficacy of buprenorphine/naloxone in elderly patients over 65 years of age have not been established. No recommendation on posology can be made.

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 section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).
Both active substances of Suboxone, buprenorphine and naloxone, are extensively metabolized 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 buprenorphine/naloxone 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. Buprenorphine/naloxone is contraindicated in patients with severe hepatic impairment. (see section 4.3 and 5.2).

Renal impairment
Modification of the buprenorphine/naloxone dose is not required in patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4 and 5.2).

Paediatric population
The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established. No data are available.

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 section 4.4). The tablet is to be placed under the tongue until completely dissolved. Patients should not swallow or consume food or drink until the tablet is completely dissolved.

The dose is made up from multiple Suboxone tablets of different strengths, 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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Severe respiratory insufficiency
Severe hepatic impairment
Acute alcoholism or *delirium tremens*.
Concomitant administration of opioid antagonists (naltrexone, nalmefene) for the treatment of alcohol or opioid dependence.

4.4 Special warnings and precautions for use

Misuse, abuse and diversion
Buprenorphine 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 or localised and systemic infections, respiratory depression and hepatic injury. Buprenorphine misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicinal product is not safeguarded against theft.

Sub-optimal treatment with buprenorphine/naloxone may prompt medicine misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine/naloxone may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

To minimize the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, 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 needs.

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
A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines (see section 4.5) or when buprenorphine was not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and 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.

This product should be used with care in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath)).

Buprenorphine/naloxone 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
Buprenorphine/naloxone may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants (such as tranquilisers, sedatives or hypnotics) (see section 4.5).

Dependence
Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience, have demonstrated 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 addicts 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 hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, alcohol abuse, anorexia concomitant use of other potentially hepatotoxic medicines) and ongoing injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing buprenorphine/naloxone and during treatment. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.

Precipitation of opioid withdrawal syndrome
When initiating treatment with buprenorphine/naloxone, 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. Patients should be clearly monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported. To avoid precipitating withdrawal, induction with

buprenorphine/naloxone should be undertaken when objective signs of withdrawal are evident (see section 4.2).

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

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Since both buprenorphine and naloxone are extensively metabolized, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment after single-dose administration. 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 hepatic impairment (See section 4.3 and 5.2). In patients with severe hepatic insufficiency the use of buprenorphine/naloxone is contraindicated.

Renal impairment
Renal elimination may be prolonged since 30 % of the administered dose is eliminated by the renal route. 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 sections 4.2 and 5.2).

Use in adolescents (Age 15-<18)
Due to the lack of data in adolescents (age 15-<18), patients in this age group should be more closely monitored during treatment.

CYP 3A inhibitors
Medicines that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the buprenorphine/naloxone dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of buprenorphine/naloxone titrated carefully since a reduced dose may be sufficient in these patients (see section 4.5).

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, so opioids 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.

The concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine (see section 4.5).

Suboxone contains lactose. Patients with rare hereditary problems of galactose intolerance, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Suboxone should not be taken together with:

- alcoholic drinks or medicines containing alcohol, as alcohol increases the sedative effect of buprenorphine (see section 4.7).

Suboxone should be used cautiously when co-administered with:

- benzodiazepines: This combination may result in death due to respiratory depression of central origin. Therefore, dosages must be limited and this combination must 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 section 4.4).

- other central nervous system depressants, other opioid derivatives (e.g. methadone, analgesics and antitussives), certain antidepressants, sedative H_1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: these combinations increase central nervous system depression. The reduced level of alertness can make driving and using machines hazardous.

- Furthermore, adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine/naloxone. Therefore 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.

- naltrexone and nalmefene are opioid antagonists that can block the pharmacological effects of buprenorphine. Co-administration during buprenorphine/naloxone treatment is contraindicated due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms (see section 4.3).

- 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 such as ketoconazole or itraconazole, macrolide antibiotics).

- 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 buprenorphine/naloxone should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. The dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

- the concomitant use of monoamine oxidase inhibitors (MAOI) might produce exaggeration of the effects of opioids, based on experience with morphine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Suboxone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Towards the end of pregnancy buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus or convulsions). The syndrome is generally delayed from 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 buprenorphine/naloxone during pregnancy should be assessed by the physician. Buprenorphine/naloxone should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
It is unknown whether naloxone is excreted in human breast milk. Buprenorphine and its metabolites are excreted in human breast milk. In rats buprenorphine has been found to inhibit lactation. Therefore, breastfeeding should be discontinued during treatment with Suboxone.

Fertility
Animal studies have shown a reduction in female fertility at high doses (systemic exposure > 2.4 times the human exposure at the maximum recommended dose of 24 mg buprenorphine, based on AUC). See section 5.3.

4.7 Effects on ability to drive and use machines

Buprenorphine/naloxone has minor to moderate influence on the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If taken together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see sections 4.4 and 4.5).

Patients should be cautioned about driving or operating hazardous machinery in case buprenorphine/naloxone may affect their ability to engage in such activities.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported treatment related adverse reactions reported during the pivotal clinical trials were constipation and symptoms commonly associated with drug withdrawal (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 1 summarises adverse reactions reported from pivotal clinical trials in which, 342 of 472 patients (72.5 %) reported adverse reactions and adverse reactions reported during post-marketing surveillance.

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), Not known (cannot be estimated from available data).

Table 1: Treatment-related adverse reactions reported in clinical trials and post-marketing surveillance of buprenorphine/naloxone

System Organ Class	**Very common**	**Common**	**Uncommon**	**Not Known**
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	Anaphylactic shock
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	Hallucination
Nervous system disorders	Headache	Migraine Dizziness Hypertonia Paraesthesia Somnolence	Amnesia Hyperkinesia Seizure Speech disorder Tremor	Hepatic encephalopathy Syncope
Eye disorders		Amblyopia Lacrimal disorder	Conjunctivitis Miosis	
Ear and labyrinth disorders				Vertigo
Cardiac disorders			Angina Pectoris Bradycardia Myocardial infarction Palpitations Tachycardia	
Vascular disorders		Hypertension Vasodilatation	Hypotension	Orthostatic hypotension
Respiratory,		Cough	Asthma	Bronchospasm

thoracic and mediastinal disorders			Dyspnoea Yawning	Respiratory depression
Gastrointestinal disorders	Constipation Nausea	Abdominal Pain Diarrhoea Dyspepsia Flatulence Vomiting	Mouth ulceration Tongue discolouration	
Hepatobiliary disorders				Hepatitis Hepatitis acute Jaundice Hepatic necrosis Hepatorenal syndrome
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pruritus Rash Urticaria	Acne Alopecia Dermatitis exfoliative Dry skin Skin mass	Angioedema
Musculoskeletal and connective tissue disorders		Back Pain Arthralgia Muscle spasms Myalgia	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	Hypothermia	Drug withdrawal syndrome neonatal (see section 4.6)
Investigations		Liver function test abnormal Weight decreased	Blood creatinine increased	Transaminases increased
Injury, poisoning and procedural complications		Injury	Heat stroke	

Description of selected adverse reactions

In cases of intravenous drug misuse, some adverse experiences are attributed to the act of misuse rather than the medicinal product and include local reactions, sometimes septic (abscess, cellulitis),

and potentially serious acute hepatitis and other acute infections such as pneumonia, endocarditis have been reported (see section 4.4).

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a drug withdrawal syndrome similar to that associated with naloxone (see sections 4.2 and 4.4).

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Respiratory depression as a result of central nervous system depression is the primary symptom requiring intervention in the case of overdose because it may lead to respiratory arrest and death. Signs of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and/or speech disorders.

Management
General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, and standard intensive care measures, should be implemented. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

If the patient vomits, care must be taken to prevent aspiration of the vomitus.

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.

If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance 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. Initial naloxone doses may range up to 2 mg and be repeated every 2-3 minutes until a satisfactory response is achieved, but should not exceed a 10 mg starting dose. Ongoing intravenous infusion rates should be titrated to patient response.

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 an opioid partial agonist/antagonist which binds to the μ and κ (kappa) opioid receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible

properties with the μ-opioid receptors which, over a prolonged period, might minimise the need of addicted patients for drugs.

Opioid agonist ceiling effects were observed during clinical pharmacology studies in opioid-dependent persons.

Naloxone is an antagonist at μ-opioid receptors. When administered orally or sublingually in usual doses to patients experiencing opioid withdrawal, naloxone exhibits little or no pharmacological effect because of its almost complete first pass metabolism. 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 efficacy

Efficacy and safety data for buprenorphine/naloxone are primarily derived from a one-year clinical trial, comprising a 4-week randomised double blind comparison of buprenorphine/naloxone, buprenorphine and placebo followed by a 48 week safety study of buprenorphine/naloxone. In this trial, 326 heroin-addicted subjects were randomly assigned to either buprenorphine/naloxone 16 mg per day, 16 mg buprenorphine per day or placebo. For subjects randomized to either active treatment, dosing began with 8 mg of buprenorphine on Day 1, followed by 16 mg (two 8 mg) of buprenorphine on Day 2. On Day 3, those randomized to receive buprenorphine/naloxone 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 buprenorphine/naloxone individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both buprenorphine/naloxone 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 randomized 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 buprenorphine/naloxone), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to10 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.

5.2 Pharmacokinetic properties

Buprenorphine

Absorption

Buprenorphine, when taken orally, undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of this medicinal product by the oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration. Plasma levels of buprenorphine increased with the sublingual dose of buprenorphine/naloxone. Both C_{max} and AUC of buprenorphine increased with the increase in dose (in the range of 4-16 mg), although the increase was less than dose-proportional.

Pharmacokinetic Parameter	**Suboxone 4 mg**	**Suboxone 8 mg**	**Suboxone 16 mg**

C_{max} ng/ml	1.84 (39)	3.0 (51)	5.95 (38)
AUC_{0-48} hour ng/ml	12.52 (35)	20.22 (43)	34.89 (33)

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

Biotransformation and elimination
Buprenorphine is metabolised by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirm that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N-dealkylbuprenorphine is a μ-opioid agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri-exponential, and has a mean half-life from plasma of 32 hours.
Buprenorphine is eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70 %), the rest being eliminated in the urine.

Naloxone

Absorption and distribution:
Following intravenous administration, naloxone is rapidly distributed (distribution half-life ~ 4 minutes). Following oral administration, naloxone is barely detectable in plasma; following sublingual administration of buprenorphine/naloxone, plasma naloxone concentrations are low and decline rapidly.

Biotransformation
The medicinal product is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone has a mean half-life from plasma of 1.2 hours.

Special populations

Elderly
No pharmacokinetic data in elderly patients are available.

Renal impairment
Renal elimination plays a relatively small role (~30 %) in the overall clearance of buprenorphine/naloxone. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment (see Section 4.3).

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study.

Table 3 summarizes the results from a clinical trial in which the exposure after single-dose administration of Suboxone 2.0/0.5mg (buprenorphine/naloxone) sublingual tablet was determined in healthy subjects, and in subjects with hepatic impairment.

Table 3. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following SUBOXONE 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.

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.

Reproduction studies by oral administration of buprenorphine: naloxone (ratio 1:1) indicated that embryolethality occurred in rats in the presence of maternal toxicity at all doses. The lowest dose studied represented exposure multiples of 1x for buprenorphine and 5x for naloxone at the maximum human therapeutic dose calculated on a mg/m² basis. No developmental toxicity was observed in rabbits at maternally toxic doses. Further, no teratogenicity has been observed in either rats or rabbits. A peri-postnatal study has not been conducted with buprenorphine/naloxone; however, maternal oral administration of buprenorphine at high doses during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm

(estimated exposure approximately 2.4x for buprenorphine at a human dose of 24 mg buprenorphine/naloxone based on AUC, plasma levels of naloxone were below the limit of detection in rats) had no adverse effect on fertility in females.

A carcinogenicity study with buprenorphine/naloxone 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/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol
Maize starch
Povidone K 30
Citric acid anhydrous
Sodium citrate
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

This medicinal product does not require any special storage conditions.

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.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Indivior UK Limited
103 – 105 Bath Road
Slough
Berkshire
SL1 3UH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/003
EU/1/06/359/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 26 September 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 16 mg/4 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 16 mg buprenorphine (as hydrochloride) and 4 mg naloxone (as hydrochloride dihydrate).

Excipients with known effect:
Each sublingual tablet contains 156.64 mg lactose (as monohydrate)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

White round biconvex tablets of 10.5 mm with “N16” debossed on one side.

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

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

Precautions to be taken before induction
Prior to treatment initiation, 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 of opioid dependence. To avoid precipitating withdrawal, induction with buprenorphine/naloxone or buprenorphine only should be undertaken when objective and clear signs of withdrawal are evident (demonstrated e.g. by a score indicating mild to moderate withdrawal on the validated Clinical Opioid Withdrawal Scale, COWS).

- For patients dependent upon heroin or short-acting opioids, the first dose of buprenorphine/naloxone should be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.
- For patients receiving methadone, the dose of methadone should be reduced to a maximum of 30 mg/day before beginning buprenorphine/naloxone therapy. The long half life of methadone should be considered when starting buprenorphine/naloxone. The first dose of buprenorphine/naloxone should be taken only when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

Posology

Initiation therapy (induction)
The recommended starting dose in adults and adolescents over 15 years of age is one to two Suboxone 2 mg/0.5 mg. An additional one to two Suboxone 2 mg/0.5 mg may be administered on day one depending on the individual patient's requirement.
During the initiation of treatment, daily supervision of dosing 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 therapy
Following treatment induction on day one, the patient should be stabilised to a maintenance dose during the next few days by progressively adjusting the dose according to the clinical effect of the individual patient. Dose titration in steps of 2-8 mg buprenorphine is guided by reassessment of the clinical and psychological status of the patient, and should not exceed a maximum single daily dose of 24 mg buprenorphine.

Less than daily dosing
After a satisfactory 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 buprenorphine may be given 16 mg buprenorphine on alternate days, with no dose on the intervening days. In some patients, after a satisfactory 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 dose on the intervening days. However, the dose given on any one day should not exceed 24 mg buprenorphine. Patients requiring a titrated daily dose> 8 mg buprenorphine/day may not find this regimen adequate.

Medical withdrawal
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 doses of 2 mg/0.5 mg and 8 mg/2 mg allows for a downward titration of dosage. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg may be used. Patients should be monitored following medical withdrawal because of the potential for relapse.

<u>Special populations</u>

Elderly
The safety and efficacy of buprenorphine/naloxone in elderly patients over 65 years of age have not been established. No recommendation on posology can be made.

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 section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).
Both active substances of Suboxone, buprenorphine and naloxone, are extensively metabolized 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 buprenorphine/naloxone 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. Buprenorphine/naloxone is contraindicated in patients with severe hepatic impairment (see section 4.3 and 5.2).

Renal impairment

Modification of the buprenorphine/naloxone dose is not required in patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4 and 5.2).

Paediatric population
The safety and efficacy of buprenorphine/naloxone in children below the age of 15 years have not been established. No data are available.

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 section 4.4). The tablet is to be placed under the tongue until completely dissolved. Patients should not swallow or consume food or drink until the tablet is completely dissolved.

The dose can be made up from multiple Suboxone tablets of different strengths, 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.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Severe respiratory insufficiency
Severe hepatic impairment
Acute alcoholism or *delirium tremens*.
Concomitant administration of opioid antagonists (naltrexone, nalmefene) for the treatment of alcohol or opioid dependence.

4.4 Special warnings and precautions for use

Misuse, abuse and diversion
Buprenorphine 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 or localised and systemic infections, respiratory depression and hepatic injury. Buprenorphine misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicinal product is not safeguarded against theft.

Sub-optimal treatment with buprenorphine/naloxone may prompt medicine misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine/naloxone may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

To minimize the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, 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 needs.

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
A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines (see section 4.5) or when buprenorphine was not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and 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.

This product should be used with care in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath)).

Buprenorphine/naloxone 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
Buprenorphine/naloxone may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants (such as tranquilisers, sedatives or hypnotics) (see section 4.5).

Dependence
Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience, have demonstrated 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 addicts 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 hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines) and ongoing injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing buprenorphine/naloxone and during treatment. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.

Precipitation of opioid withdrawal syndrome
When initiating treatment with buprenorphine/naloxone, 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. Patients should be clearly monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported. To avoid precipitating withdrawal, induction with buprenorphine/naloxone should be undertaken when objective signs of withdrawal are evident (see section 4.2).

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

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Since both buprenorphine and naloxone are extensively metabolized, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment after single-dose administration. 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 hepatic impairment (See section 4.3 and 5.2). In patients with severe hepatic insufficiency the use of buprenorphine/naloxone is contraindicated.

Renal impairment
Renal elimination may be prolonged since 30 % of the administered dose is eliminated by the renal route. 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 sections 4.2 and 5.2).

Use in adolescents (Age 15-<18)
Due to the lack of data in adolescents (age 15-<18), patients in this age group should be more closely monitored during treatment.

CYP 3A inhibitors
Medicines that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the buprenorphine/naloxone dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of buprenorphine/naloxone titrated carefully since a reduced dose may be sufficient in these patients (see section 4.5).

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, so opioids 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.

The concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine (see section 4.5).

Suboxone contains lactose. Patients with rare hereditary problems of galactose intolerance, should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Suboxone should not be taken together with:

- alcoholic drinks or medicines containing alcohol, as alcohol increases the sedative effect of buprenorphine (see section 4.7).

Suboxone should be used cautiously when co-administered with:

- benzodiazepines: This combination may result in death due to respiratory depression of central origin. Therefore, dosages must be limited and this combination must 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 section 4.4).

- other central nervous system depressants, other opioid derivatives (e.g. methadone, analgesics and antitussives), certain antidepressants, sedative H_1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances: these combinations increase central nervous system depression. The reduced level of alertness can make driving and using machines hazardous.

- Furthermore, adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine/naloxone. Therefore 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.

- naltrexone and nalmefene are opioid antagonists that can block the pharmacological effects of buprenorphine. Co-administration during buprenorphine/naloxone treatment is contraindicated due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms (see section 4.3).

- 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 such as ketoconazole or itraconazole, macrolide antibiotics).

- 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 buprenorphine/naloxone should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. The dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

- the concomitant use of monoamine oxidase inhibitors (MAOI) might produce exaggeration of the effects of opioids, based on experience with morphine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Suboxone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Towards the end of pregnancy buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate (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.

Furthermore, the use of buprenorphine/naloxone during pregnancy should be assessed by the physician. Buprenorphine/naloxone should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
It is unknown whether naloxone is excreted in human breast milk. Buprenorphine and its metabolites are excreted in human breast milk. In rats buprenorphine has been found to inhibit lactation. Therefore, breastfeeding should be discontinued during treatment with Suboxone.

Fertility
Animal studies have shown a reduction in female fertility at high doses (systemic exposure > 2.4 times the human exposure at the maximum recommended dose of 24 mg buprenorphine, based on AUC). See section 5.3.

4.7 Effects on ability to drive and use machines

Buprenorphine/naloxone has minor to moderate influence on the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If taken together with alcohol or central nervous system depressants, the effect is likely to be more pronounced (see sections 4.4 and 4.5).

Patients should be cautioned about driving or operating hazardous machinery in case buprenorphine/naloxone may affect their ability to engage in such activities.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported treatment related adverse reactions reported during the pivotal clinical trials were constipation and symptoms commonly associated with drug withdrawal (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 1 summarises adverse reactions reported from pivotal clinical trials in which, 342 of 472 patients (72.5 %) reported adverse reactions and adverse reactions reported during post-marketing surveillance.

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), Not known (cannot be estimated from available data).

Table 1: Treatment-related adverse reactions reported in clinical trials and post- marketing surveillance of buprenorphine/naloxone

System Organ Class	Very common	Common	Uncommon	Not known
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	Anaphylactic shock
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	Hallucination
Nervous system disorders	Headache	Migraine Dizziness Hypertonia Paraesthesia Somnolence	Amnesia Hyperkinesia Sezuire Speech disorder Tremor	Hepatic encepalopathy Syncope
Eye disorders		Amblyopia Lacrimal disorder	Conjunctivitis Miosis	
Ear and labyrinth disorders				Vertigo
Cardiac disorders			Angina Pectoris Bradycardia Myocardial infarction Palpitations Tachycardia	
Vascular disorders		Hypertension Vasodilatation	Hypotension	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		Cough	Asthma Dyspnoea Yawning	Bronchospasm Respiratory depression
Gastrointestinal disorders	Constipation Nausea	Abdominal Pain Diarrhoea Dyspepsia Flatulence Vomiting	Mouth ulceration Tongue discolouration	

Hepatobiliary disorders				Hepatitis Hepatitis acute Jaundice Hepatic necrosis Hepatorenal syndrome
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pruritus Rash Urticaria	Acne Alopecia Dermatitis exfoliative Dry skin Skin mass	Angioedema
Musculoskeletal and connective tissue disorders		Back Pain Arthralgia Muscle spasms Myalgia	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	Hypothermia	Drug withdrawal syndrome neonatal (see section 4.6)
Investigations		Liver function test abnormal Weight decreased	Blood creatinine increased	Transaminases increased
Injury, poisoning and procedural complications		Injury	Heat stroke	

Description of selected adverse reactions

In cases of intravenous drug misuse, some adverse experiences are attributed to the act of misuse rather than the medicinal product and include local reactions, sometimes septic (abscess, cellulitis), and potentially serious acute hepatitis, and other acute infections such as pneumonia, endocarditis have been reported (see section 4.4).

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a drug withdrawal syndrome similar to that associated with naloxone (see sections 4.2 and 4.4).

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Respiratory depression as a result of central nervous system depression is the primary symptom requiring intervention in the case of overdose because it may lead to respiratory arrest and death. Signs of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and/or speech disorders.

Management
General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, and standard intensive care measures, should be implemented. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

If the patient vomits, care must be taken to prevent aspiration of the vomitus.

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.

If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance 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. Initial naloxone doses may range up to 2 mg and be repeated every 2-3 minutes until a satisfactory response is achieved, but should not exceed a 10 mg starting dose. Ongoing intravenous infusion rates should be titrated to patient response.

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 an opioid partial agonist/antagonist which binds to the μ and κ (kappa) opioid receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the μ-opioid receptors which, over a prolonged period, might minimise the need of addicted patients for drugs.

Opioid agonist ceiling effects were observed during clinical pharmacology studies in opioid-dependent persons.

Naloxone is an antagonist at μ-opioid receptors. When administered orally or sublingually in usual doses to patients experiencing opioid withdrawal, naloxone exhibits little or no pharmacological effect because of its almost complete first pass metabolism. 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 efficacy

Efficacy and safety data for buprenorphine/naloxone are primarily derived from a one-year clinical trial, comprising a 4-week randomised double blind comparison of buprenorphine/naloxone, buprenorphine and placebo followed by a 48 week safety study of buprenorphine/naloxone. In this trial, 326 heroin-addicted subjects were randomly assigned to either buprenorphine/naloxone 16 mg per day, 16 mg buprenorphine per day or placebo. For subjects randomized to either active treatment, dosing began with 8 mg of buprenorphine on Day 1, followed by 16 mg (two 8 mg) of buprenorphine on Day 2. On Day 3, those randomized to receive buprenorphine/naloxone 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 buprenorphine/naloxone individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both buprenorphine/naloxone 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 randomized 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 buprenorphine/naloxone), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to10 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.

5.2 Pharmacokinetic properties

Buprenorphine

Absorption

Buprenorphine, when taken orally, undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of this medicinal product by the oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration. Plasma levels of buprenorphine increased with the sublingual dose of buprenorphine/naloxone. Both C_{max} and AUC of buprenorphine increased with the increase in dose (in the range of 4-16 mg), although the increase was less than dose-proportional.

Pharmacokinetic Parameter	**Suboxone 4 mg**	**Suboxone 8 mg**	**Suboxone 16 mg**
C_{max} ng/ml	1.84 (39)	3.0 (51)	5.95 (38)
AUC_{0-48} hour ng/ml	12.52 (35)	20.22 (43)	34.89 (33)

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

Biotransformation and elimination
Buprenorphine is metabolised by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirm that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N-dealkylbuprenorphine is a μ-opioid agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri-exponential, and has a mean half-life from plasma of 32 hours.
Buprenorphine is eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70 %), the rest being eliminated in the urine.

Naloxone

Absorption and distribution
Following intravenous administration, naloxone is rapidly distributed (distribution half-life ~ 4 minutes). Following oral administration, naloxone is barely detectable in plasma; following sublingual administration of buprenorphine/naloxone, plasma naloxone concentrations are low and decline rapidly.

Biotransformation
The medicinal product is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone has a mean half-life from plasma of 1.2 hours.

Special populations

Elderly
No pharmacokinetic data in elderly patients are available.

Renal impairment
Renal elimination plays a relatively small role (~30 %) in the overall clearance of buprenorphine/naloxone. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment (see Section 4.3).

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study.

Table 3 summarizes the results from a clinical trial in which the exposure after single-dose administration of Suboxone 2.0/0.5mg (buprenorphine/naloxone) sublingual tablet was determined in healthy subjects, and in subjects with hepatic impairment.

Table 3. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone following SUBOXONE 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.

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.

Reproduction studies by oral administration of buprenorphine: naloxone (ratio 1:1) indicated that embryolethality occurred in rats in the presence of maternal toxicity at all doses. The lowest dose studied represented exposure multiples of 1x for buprenorphine and 5x for naloxone at the maximum human therapeutic dose calculated on a mg/m² basis. No developmental toxicity was observed in rabbits at maternally toxic doses. Further, no teratogenicity has been observed in either rats or rabbits. A peri-postnatal study has not been conducted with buprenorphine/naloxone; however, maternal oral administration of buprenorphine at high doses during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (estimated exposure approximately 2.4x for buprenorphine at a human dose of 24 mg buprenorphine/naloxone based on AUC, plasma levels of naloxone were below the limit of detection in rats) had no adverse effect on fertility in females.

A carcinogenicity study with buprenorphine/naloxone 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/m² basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol
Maize starch
Povidone K 30
Citric acid anhydrous
Sodium citrate
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

This medicinal product does not require any special storage conditions.

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.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Indivior UK Limited
103 – 105 Bath Road
Slough

Berkshire
SL1 3UH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/005
EU/1/06/359/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 26 September 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Reckitt Benckiser Healthcare (UK) Ltd
Dansom Lane
Hull, East Yorkshire
HU8 7DS
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 7 and 28 TABLETS 2 mg STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 2 mg/0.5 mg sublingual tablets
buprenorphine/naloxone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

7 sublingual tablets
28 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use
Do not swallow.
Keep the tablet under your tongue until it dissolves.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited
103-105 Bath Road
Slough, Berkshire SL1 3UH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/001 2 mg sublingual tablets 7
EU/1/06/359/002 2 mg sublingual tablets 28

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Suboxone 2 mg/0.5 mg sublingual tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PACK OF 7 and 28 TABLETS 2 mg STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 2 mg/0.5 mg sublingual tablets
buprenorphine / naloxone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 7 and 28 TABLETS 8 mg STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 8 mg/2 mg sublingual tablets
buprenorphine/naloxone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 8 mg buprenorphine as buprenorphine hydrochloride and 2 mg naloxone as naloxone hydrochloride dihydrate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

7 sublingual tablets
28 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use
Do not swallow.
Keep the tablet under your tongue until it dissolves.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited
103-105 Bath Road
Slough, Berkshire SL1 3UH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/003 8 mg sublingual tablets 7
EU/1/06/359/004 8 mg sublingual tablets 28

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Suboxone 8 mg/2 mg sublingual tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PACK OF 7 and 28 TABLETS 8 mg STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 8 mg/2 mg sublingual tablets
buprenorphine / naloxone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 7 and 28 TABLETS 16 mg STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 16 mg/4 mg sublingual tablets
buprenorphine/naloxone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 16 mg buprenorphine (as hydrochloride) and 4 mg naloxone (as hydrochloride dihydrate).

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

7 sublingual tablets
28 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use
Do not swallow.
Keep the tablet under your tongue until it dissolves.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited
103-105 Bath Road
Slough, Berkshire SL1 3UH
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/005 16 mg sublingual tablets 7
EU/1/06/359/006 16 mg sublingual tablets 28

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Suboxone 16 mg/4 mg sublingual tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PACK OF 7 and 28 TABLETS 16 mg STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 16 mg/4 mg sublingual tablets
buprenorphine / naloxone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Suboxone 2 mg/0.5 mg sublingual tablets
buprenorphine / naloxone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you**.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What Suboxone is and what it is used for

Suboxone is used to treat dependence on opioid (narcotic) drugs such as heroin or morphine in drug addicts who have agreed to be treated for their addiction. Suboxone is used in adults and adolescents over 15 years of age, who are also receiving medical, social and psychological support.

2. What you need to know before you take Suboxone

Do not take Suboxone

- if you are allergic (hypersensitive) to buprenorphine, naloxone or any of the other ingredients of this medicine (see section 6)
- if you have **serious breathing problems**
- if you have **serious liver problems**
- if you are intoxicated due to alcohol or have trembling, sweating, anxiety, confusion, or hallucinations caused by alcohol.
- if you are taking naltrexone or nalmefene for the treatment of alcohol or opioid dependence.

Warnings and precautions

Talk to your doctor before taking Suboxone if you have:

- asthma or other breathing problems
- any liver disease such as hepatitis
- low blood pressure
- recently suffered a head injury or brain disease
- a urinary disorder (especially linked to enlarged prostrate in men)
- any kidney disease
- thyroid problems
- adrenocortical disorder (e.g. Addison’s disease)

Important things to be aware of:

- **Additional monitoring**
  You may be more closely monitored by your doctor if you are below the age of 18 or over the age of 65. This medicine should not be taken by those under 15 years of age.

- **Misuse and abuse**
  This medicine can be a target for people who abuse prescription medicines, and should be kept in a safe place to protect it from theft. **Do not give this medicine to anyone else**. It can cause death or otherwise harm them.

- **Breathing problems**
  Some people have died from respiratory failure (inability to breathe) because they misused this medicine or took it in combination with other central nervous system depressants, such as alcohol, benzodiazepines (tranquilisers), or other opioids.

  This medicine may cause severe, possibly fatal, respiratory depression (reduced ability to breathe) in children and non-dependent people who accidentally or deliberately take it.

- **Dependence**
  This product can cause dependence.

- **Withdrawal symptoms**
  This product can cause withdrawal symptoms if you take it less than six hours after you use a short-acting opioid (e.g. morphine, heroin) or less than 24 hours after you use a long-acting opioid such as methadone.

  Suboxone can also cause withdrawal symptoms if you stop taking it abruptly.

- **Liver damage**
  Liver damage has been reported after taking Suboxone, especially when the medicine is misused. This could also be due to viral infections (chronic hepatitis C), alcohol abuse, anorexia or use of other medicines with the ability to harm your liver (see section 4). **Regular blood tests may be conducted by your doctor to monitor the condition of your liver. Tell your doctor if you have any liver problems before you start treatment with Suboxone.**

- **Blood pressure**
  This product may cause your blood pressure to drop suddenly, causing you to feel dizzy if you get up too quickly from sitting or lying down.

- **Diagnosis of unrelated medical conditions**
  This medicine may mask pain symptoms that could assist in the diagnosis of some diseases. Do not forget to advise your doctor if you take this medicine.

Other medicines and Suboxone
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Some medicines may increase the side effects of Suboxone and may sometimes cause very serious reactions. Do not take any other medicines whilst taking Suboxone without first talking to your doctor, especially:

- **Benzodiazepines** (used to treat anxiety or sleep disorders) such as diazepam, temazepam, alprazolam. Your doctor will prescribe the correct dose for you. **Taking the wrong dose of benzodiazepines may cause death due to respiratory failure (inability to breathe).**

- **Other medicines that may make you feel sleepy which are** used to treat illnesses such as anxiety, sleeplessness, convulsions/seizures, pain. These types of medicines will reduce your alertness levels making it difficult for you to drive and use machines. They may also cause central nervous system depression, which is very serious. Below is a list of examples of these types of medicines:

- other opioid containing medicines such as methadone, certain pain killers and cough suppressants
- anti-depressants (used to treat depression) such as isocarboxazid, phenelzine, selegiline, tranylcypromine and valproate may increase the effects of this medicine.
- sedative Hı receptor antagonists (used to treat allergic reactions) such as diphenhydramine and chlorphenamine.
- barbiturates (used to cause sleep or sedation) such as Phenobarbital, secobarbital
- tranquilisers (used to cause sleep or sedation) such as chloral hydrate.

- clonidine (used to treat high blood pressure) may extend the effects of this medicine.
- anti-retrovirals (used to treat HIV) such as ritonavir, nelfinavir, indinavir may increase the effects of this medicine.
- some antifungal agents (used to treat fungal infections) such as ketoconazole, itraconazole, certain antibiotics, may extend the effects of this medicine.
- some medicines may decrease the effect of Suboxone. These include medicines used to treat epilepsy (such as carbamazepine and phenytoin), and medicines used to treat tuberculosis (rifampicin).
- Naltrexone and nalmefene (drugs used to treat addiction disorders) may prevent the therapeutic effects of Suboxone. They should not be taken at the same time as Suboxone treatment because you may experience a sudden onset of prolonged and intense withdrawal.

Suboxone with food, drink and alcohol
Alcohol may increase drowsiness and may increase the risk of respiratory failure if taken with Suboxone. **Do not take Suboxone together with alcohol.** Do not swallow or consume food or any drink until the tablet is completely dissolved.

Pregnancy and breast-feeding
The risks of using Suboxone in pregnant women are not known. Tell your doctor if you are pregnant or intend to become pregnant. Your doctor will decide if your treatment should be continued with an alternative medicine.

When taken during pregnancy, particularly late pregnancy, medicines like Suboxone may cause drug withdrawal symptoms including problems with breathing in your newborn baby. This may appear several days after birth.

Do not breast-feed whilst taking this medicine, since Suboxone passes into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Suboxone may cause drowsiness. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative medicines when you take Suboxone. Do not drive, use any tools or machines, or perform dangerous activities until you know how this medicine affects you.

Suboxone contains lactose
If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Suboxone

Your treatment is prescribed and monitored by doctors who are experienced in the treatment of drug dependence.

Your doctor will determine the best dose for you. During your treatment, the doctor may adjust the dose, depending upon your response.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Starting treatment

The recommended starting dose for adults and adolescents over the age of 15 years is one to two tablets of Suboxone 2 mg/0.5 mg. An additional one to two tablets of the Suboxone 2 mg/0.5 mg may be administered on day 1 depending on your needs.

Clear signs of withdrawal should be evident before taking your first dose of Suboxone. A doctor's assessment of your readiness for treatment will guide the timing of your first Suboxone dose.

- Starting treatment of Suboxone whilst dependent on heroin

  If you are dependent upon heroin or a short acting opioid, your first dose of Suboxone should be taken when signs of withdrawal appear, but not less than 6 hours after you last used opioids.

- Starting treatment of Suboxone whilst dependent on methadone

  If you have been taking methadone or a long acting opioid, the dose of methadone should ideally be reduced to below 30 mg/day before beginning Suboxone therapy. The first dose of Suboxone should be taken when signs of withdrawal appear, but not less than 24 hours after you last used methadone.

Taking Suboxone

- Take the dose once a day by placing the tablets under the tongue.

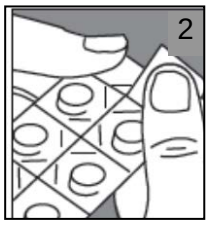
- Keep the tablets in place under the tongue until they have **completely dissolved**. This may take 5-10 minutes.

- Do not chew or swallow the tablets, as the medicine will not work and you may get withdrawal symptoms.

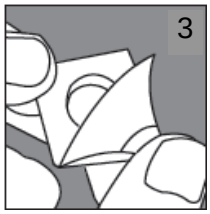
Do not consume any food or drink until the tablets have completely dissolved.

How to remove the tablet from the blister

1 - Do not push the tablet through the foil.



2 - Remove just one section from the blister pack, tearing it along the perforated line.



3 – Starting from the edge where the seal is lifted, pull back the foil on the back to remove the tablet

If the blister is damaged, discard the tablet

Dosage adjustment and maintenance therapy:

During the days after you start treatment, your doctor may increase the dose of Suboxone you take according to your needs. If you have the impression that the effect of Suboxone is too strong or too weak, talk to your doctor or pharmacist. The maximum daily dose is 24 mg.

After a time of successful treatment, you may agree with your doctor to reduce the dose gradually to a lower maintenance dose.

Stopping treatment

Depending on your condition, the dose of Suboxone may continue to be reduced under careful medical supervision, until eventually it may be stopped.

Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you.

If you take more Suboxone than you should
If you or someone else takes too much of this medicine, you must go or be taken immediately to an emergency centre or hospital for treatment as **overdose** with Suboxone may cause serious and life-threatening breathing problems.
Symptoms of overdose may include feeling sleepy and uncoordinated with slowed reflexes, blurred vision, and/or slurred speech. You may be unable to think clearly, and may breathe much slower than is normal for you.

If you forget to take Suboxone
Tell your doctor as soon as possible if you miss a dose.

If you stop taking Suboxone
Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you. **Stopping treatment suddenly may cause withdrawal symptoms.**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Suboxone can cause side effects, although not everybody gets them.

Tell your doctor immediately or seek urgent medical attention if you experience side effects, such as:

- swelling of the face, lips, tongue or throat which may cause difficulty in swallowing or breathing, severe hives/nettle rash. These may be signs of a life-threatening allergic reaction.
- feeling sleepy and uncoordinated, have blurred vision, have slurred speech, cannot think well or clearly, or your breathing gets much slower than is normal for you.

Also tell your doctor immediately if you experience side effects such as:

- severe tiredness, itching with yellowing of skin or eyes. These may be symptoms of liver damage.
- seeing or hearing things that are not there (hallucinations).

Side effects reported with Suboxone
Very common side effects (may effect more than one in 10 people):
Insomnia (inability to sleep), constipation, nausea, excessive sweating, headache, drug withdrawal syndrome
Common side effects (may effect up to 1 in 10 people):
Weight loss, swelling (hands and feet), drowsiness, anxiety, nervousness, tingling, depression, decreased sexual drive, increase in muscle tension, abnormal thinking, increased tearing (watering eyes) or other tearing disorder, blurred vision, flushing, increased blood pressure, migraines, runny nose, sore throat and painful swallowing, increased cough, upset stomach or other stomach discomfort, diarrhoea, abnormal liver function, flatulence, vomiting, rash, itching, hives, pain, joint pain, muscle pain, leg cramps (muscle spasm), difficulty in getting or keeping an erection, urine abnormality, abdominal pain, back pain, weakness, infection, chills, chest pain, fever, flu-like symptoms, feeling of general discomfort, accidental injury caused by loss of alertness or co-ordination, faintness and dizziness.
Uncommon side effects (may effect up to 1 in 100 people):
Swollen glands (lymph nodes), agitation, tremor, abnormal dream, excessive muscle activity, depersonalisation (not feeling like yourself), medicine dependence, amnesia (memory disturbance), loss of interest, exaggerated feeling of well being, convulsion (fits), speech disorder, small pupil size, difficulty urinating, eye inflammation or infection, rapid or slow heart beat, low blood pressure, palpitations, myocardial infarction (heart attack), chest tightness, shortness of breath, asthma, yawning, pain and sores in mouth, tongue discolouration, acne, skin nodule, hair loss, dry or scaling skin, inflammation of joints, urinary tract infection, abnormal blood tests, blood in urine, abnormal ejaculation, menstrual or vaginal problems, kidney stone, protein in your urine, painful or difficult urination, sensitivity to heat or cold, heat stroke, loss of appetite, feelings of hostility.
Not known (frequency cannot be estimated from the available data):
Sudden withdrawal syndrome caused by taking Suboxone too soon after use of illicit opioids,

drug withdrawal syndrome in newborn. Slow or difficult breathing, liver injury with or without jaundice, hallucinations, swelling of face and throat or life threatening allergic reactions, drop in blood pressure on changing position from sitting or lying down to standing.
Misusing this medicine by injecting it can cause withdrawal symptoms, infections, other skin reactions and potentially serious liver problems (see Warnings and precautions).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Suboxone

Keep out of the sight and reach of children and other household members.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month

This medicinal product does not require any special storage conditions. However, Suboxone can be a target for people who abuse prescription medicine. Keep this medicine in a safe place to protect it from theft.

Store the blister safely.
Never open the blister in advance.
Do not take this medicine in front of children.
An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Content of the pack and other Information

What Suboxone contains

- The active substances are buprenorphine and naloxone.
  Each 2 mg/0.5 mg sublingual tablet contains 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate).
- The other ingredients are lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium and natural lemon and lime flavour.

What Suboxone looks like and contents of the pack

Suboxone 2 mg/0.5 mg sublingual tablets are white hexagonal biconvex tablets of 6.5 mm with “N2” debossed on one side.
Packed in packs of 7 and 28 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
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Manufacturer
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For any information about this medicine, please contact the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu/

Package leaflet: Information for the user

Suboxone 8 mg/2 mg sublingual tablets
buprenorphine / naloxone

Read all of this leaflet carefully before you start taking this because it contains important information for you**.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What Suboxone is and what it is used for

Suboxone is used to treat dependence on opioid (narcotic) drugs such as heroin or morphine in drug addicts who have agreed to be treated for their addiction. Suboxone is used in adults and adolescents over 15 years of age, who are also receiving medical, social and psychological support.

2. What do you need to know before you take Suboxone

Do not take Suboxone

- if you are allergic (hypersensitive) to buprenorphine, naloxone or any of the other ingredients of this medicine (see section 6)
- if you have **serious breathing problems**
- if you have **serious liver problems**
- if you are intoxicated due to alcohol or have trembling, sweating, anxiety, confusion, or hallucinations caused by alcohol
- if you are taking naltrexone or nalmefene for the treatment of alcohol or opioid dependence.

Warnings and precautions

Talk to your doctor before taking Suboxone if you have:

- asthma or other breathing problems
- any liver disease such as hepatitis
- low blood pressure
- recently suffered a head injury or brain disease
- a urinary disorder (especially linked to enlarge prostrate in men)
- any kidney disease.
- thyroid problems
- adrenocortical disorder (e.g. Addison’s disease)

Important things to be aware of:

- **Additional monitoring**
  You may be more closely monitored by your doctor if you are below the age of 18 or over the age of 65. This medicine should not be taken by those under 15 years of age.

- **Misuse and abuse**
  This medicine can be a target for people who abuse prescription medicines, and should be kept in a safe place to protect it from theft. **Do not give this medicine to anyone else**. It can cause death or otherwise harm them.

- **Breathing problems**
  Some people have died from respiratory failure (inability to breathe) because they misused this medicine or took it in combination with other central nervous system depressants, such as alcohol, benzodiazepines (tranquilisers), or other opioids.

  This medicine may cause severe, possibly fatal, respiratory depression (reduced ability to breathe) in children and non-dependent people who accidentally or deliberately take it.

- **Dependence**
  This product can cause dependence.

- **Withdrawal symptoms**
  This product can cause withdrawal symptoms if you take it less than six hours after you use a short-acting opioid (e.g. morphine, heroin) or less than 24 hours after you use a long-acting opioid such as methadone.

  Suboxone can also cause withdrawal symptoms if you stop taking it abruptly.

- **Liver damage**
  Liver damage has been reported after taking Suboxone, especially when the medicine is misused. This could also be due to viral infections (chronic hepatitis C), alcohol abuse, anorexia or use of other medicines with the ability to harm your liver (see section 4). **Regular blood tests may be conducted by your doctor to monitor the condition of your liver. Tell your doctor if you have any liver problems before you start treatment with Suboxone.**

- **Blood pressure**
  This product may cause your blood pressure to drop suddenly, causing you to feel dizzy if you get up too quickly from sitting or lying down.

- **Diagnosis of unrelated medical conditions**
  This medicine may mask pain symptoms that could assist in the diagnosis of some diseases. Do not forget to advise your doctor if you take this medicine.

Other medicines and Suboxone
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Some medicines may increase the side effects of Suboxone and may sometimes cause very serious reactions. Do not take any other medicines whilst taking Suboxone without first talking to your doctor especially:

- **Benzodiazepines** (used to treat anxiety or sleep disorders) such as, diazepam, temazepam, alprazolam. Your doctor will prescribe the correct dose for you. **Taking the wrong dose of benzodiazepines may cause death due to respiratory failure (inability to breathe).**

- **Other medicines that may make you feel sleepy which are** used to treat illnesses such as anxiety, sleeplessness, convulsions/seizures, pain. These types of medicines will reduce your alertness levels making it difficult for you to drive and use machines. They may also cause central nervous system depression, which is very serious. Below is a list of examples of these types of medicines:

- other opioid containing medicines such as methadone, certain pain killers and cough suppressants
- anti-depressants (used to treat depression) such as isocarboxazide, phenelzine, selegiline, tranylcypromine and valproate may increase the effects of this medicine.
- sedative Hı receptor antagonists (used to treat allergic reactions) such as diphenhydramine and chlorphenamine.
- barbiturates (used to cause sleep or sedation) such as Phenobarbital, secobarbital
- tranquilisers (used to cause sleep or sedation) such as chloral hydrate.

- clonidine (used to treat high blood pressure) may extend the effects of this medicine.
- anti-retrovirals (used to treat HIV) such as ritonavir, nelfinavir, indinavir may increase the effects of this medicine.
- some antifungal agents (used to treat fungal infections) such as ketoconzaole, itraconazole, certain antibiotics may extend the effects of this medicine.
- some medicines may decrease the effect of Suboxone. These include medicines used to treat epilepsy (such as carbamazepine and phenytoin), and medicines used to treat tuberculosis (rifampicin).
- naltrexone and nalmefene (drugs used to treat addiction disorders) may prevent the therapeutic effects of Suboxone. They should not be taken at the same time as Suboxone treatment because you may experience a sudden onset of prolonged and intense withdrawal.

Suboxone with food, drink and alcohol
Alcohol may increase drowsiness and may increase the risk of respiratory failure if taken with Suboxone. **Do not take Suboxone together with alcohol.** Do not swallow or consume food or any drink until the tablet is completely dissolved.

Pregnancy and breast-feeding
The risks of using Suboxone in pregnant women are not known. Tell your doctor if you are pregnant or intend to become pregnant. Your doctor will decide if your treatment should be continued with an alternative medicine.

When taken during pregnancy, particularly late pregnancy, medicines like Suboxone may cause drug withdrawal symptoms including problems with breathing in your newborn baby. This may appear several days after birth.

Do not breast-feed whilst taking this medicine, since Suboxone passes into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Suboxone may cause drowsiness. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative medicines when you take Suboxone. Do not drive, use any tools or machines, or perform dangerous activities until you know how this medicine affects you.

Suboxone contains lactose
If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Suboxone

Your treatment is prescribed and monitored by doctors who are experienced in the treatment of drug dependence.

Your doctor will determine the best dose for you. During your treatment, the doctor may adjust the dose, depending upon your response.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Starting treatment

The recommended starting dose for adults and adolescents over the age of 15 years is one to two tablets of Suboxone 2 mg/0.5 mg. An additional one to two tablets of the Suboxone 2 mg/0.5 mg may be administered on day 1 depending on your needs.

Clear signs of withdrawal should be evident before taking your first dose of Suboxone. A doctor's assessment of your readiness for treatment will guide the timing of your first Suboxone dose.

- Starting treatment of Suboxone whilst dependent on heroin

  If you are dependent upon heroin or a short acting opioid, your first dose of Suboxone should be taken when signs of withdrawal appear, but not less than 6 hours after you last used opioids.

- Starting treatment of Suboxone whilst dependent on methadone

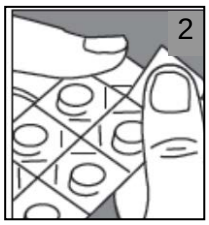
  If you have been taking methadone or a long acting opioid, the dose of methadone should ideally be reduced to below 30 mg/day before beginning Suboxone therapy. The first dose of Suboxone should be taken when signs of withdrawal appear, but not less than 24 hours after you last used methadone.

Taking Suboxone

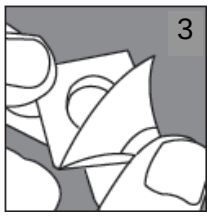
- Take the dose once a day by placing the tablets under the tongue.
- Keep the tablets in place under the tongue until they have **completely dissolved**. This may take 5-10 minutes.
- Do not chew or swallow the tablets, as the medicine will not work and you may get withdrawal symptoms.
- Do not consume any food or drink until the tablets have completely dissolved.

How to remove the tablet from the blister

1 - Do not push the tablet through the foil.



2 - Remove just one section from the blister pack, tearing it along the perforated line.



3 – Starting from the edge where the seal is lifted, pull back the foil on the back to remove the tablet

If the blister is damaged, discard the tablet

Dosage adjustment and maintenance therapy:

During the days after you start treatment, your doctor may increase the dose of Suboxone you take according to your needs. If you have the impression that the effect of Suboxone is too strong or too weak, talk to your doctor or pharmacist. The maximum daily dose is 24 .

After a time of successful treatment, you may agree with your doctor to reduce the dose gradually to a lower maintenance dose.

Stopping treatment

Depending on your condition, the dose of Suboxone may continue to be reduced under careful medical supervision, until eventually it may be stopped.

Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you.

If you take more Suboxone than you should
If you or someone else takes too much of this medicine, you must go or be taken immediately to an emergency centre or hospital for treatment as **overdose** with Suboxone may cause serious and life-threatening breathing problems.
Symptoms of overdose may include feeling sleepy and uncoordinated with slowed reflexes, blurred vision, and/or slurred speech. You may be unable to think clearly, and may breathe much slower than is normal for you.

If you forget to take Suboxone
Tell your doctor as soon as possible if you miss a dose.

If you stop taking Suboxone
Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you. **Stopping treatment suddenly may cause withdrawal symptoms.**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Suboxone can cause side effects, although not everybody gets them.

Tell your doctor immediately or seek urgent medical attention if you experience side effects, such as:

- swelling of the face, lips, tongue or throat which may cause difficulty in swallowing or breathing, severe hives/nettle rash. These may be signs of a life-threatening allergic reaction.
- feeling sleepy and uncoordinated, have blurred vision, have slurred speech, cannot think well or clearly, or your breathing gets much slower than is normal for you.

Also tell your doctor immediately if you experience side effects such as:

- severe tiredness, itching with yellowing of skin or eyes. These may be symptoms of liver damage.
- seeing or hearing things that are not there (hallucinations).

Side effects reported with Suboxone
Very common side effects(may effect more than one in 10 people):
Insomnia (inability to sleep), constipation, nausea, excessive sweating, headache, drug withdrawal syndrome
Common side effects (may effect up to 1 in 10 people):
Weight loss, swelling (hands and feet), drowsiness, anxiety, nervousness, tingling, depression, decreased sexual drive, increase in muscle tension, abnormal thinking, increased tearing (watering eyes) or other tearing disorder, blurred vision, flushing, increased blood pressure, migraines, runny nose, sore throat and painful swallowing, increased cough, upset stomach or other stomach discomfort, diarrhoea, abnormal liver function, flatulence, vomiting, rash, itching, hives, pain, joint pain, muscle pain, leg cramps (muscle spasm), difficulty in getting or keeping an erection, urine abnormality, abdominal pain, back pain, weakness, infection, chills, chest pain, fever, flu-like symptoms, feeling of general discomfort, accidental injury caused by loss of alertness or co-ordination, faintness and dizziness.
Uncommon side effects (may effect up to 1 in 100 people):
Swollen glands (lymph nodes), agitation, tremor, abnormal dream, excessive muscle activity, depersonalisation (not feeling like yourself), medicine dependence, amnesia (memory disturbance), loss of interest, exaggerated feeling of well being, convulsion (fits), speech disorder, small pupil size, difficulty urinating, eye inflammation or infection, rapid or slow heart beat, low blood pressure, palpitations, myocardial infarction (heart attack), chest tightness, shortness of breath, asthma, yawning, pain and sores in mouth, tongue discolouration, acne, skin nodule, hair loss, dry or scaling skin, inflammation of joints, urinary tract infection, abnormal blood tests, blood in urine, abnormal ejaculation, menstrual or vaginal problems, kidney stone, protein in your urine, painful or difficult urination, sensitivity to heat or cold, heat stroke, loss of appetite feelings of hostility.
Not known (frequency cannot be estimated from the available data):
Sudden withdrawal syndrome caused by taking Suboxone too soon after use of illicit opioids, drug withdrawal syndrome in newborn. Slow or difficult breathing, liver injury with or without jaundice, hallucinations, swelling of face and throat or life threatening allergic reactions, drop in blood pressure on changing position from sitting or lying down to standing. Misusing this medicine by injecting it can cause withdrawal symptoms, infections, other skin

reactions and potentially serious liver problems (see Warnings and precautions).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Suboxone

Keep out of the sight and reach of children and other household members.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month

This medicinal product does not require any special storage conditions. However, Suboxone can be a target for people who abuse prescription medicine. Keep this medicine in a safe place to protect it from theft.

Store the blister safely.
Never open the blister in advance.
Do not take this medicine in front of children.
An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Content of the pack and other Information

What Suboxone contains

- The active substances are buprenorphine and naloxone.
  Each 8 mg/2 mg tablet contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate).
- The other ingredients are lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium and natural lemon and lime flavour.

What Suboxone looks like and contents of the pack

Suboxone 8 mg/2 mg sublingual tablets are white hexagonal biconvex tablets of 11 mm with “N8” debossed on one side.
Packed in packs of 7 and 28 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Indivior UK Limited
103-105 Bath Road
Slough
Berkshire SL1 3UH
United Kingdom
Tel. + 800 270 81 901

Manufacturer
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Dansom Lane,
Hull,
East Yorkshire HU8 7DS,
United Kingdom.

For any information about this medicine, please contact the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu/

Package leaflet: Information for the user

Suboxone 16 mg/4 mg sublingual tablets
buprenorphine / naloxone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you**.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Suboxone is and what it is used for

Suboxone is used to treat dependence on opioid (narcotic) drugs such as heroin or morphine in drug addicts who have agreed to be treated for their addiction. Suboxone is used in adults and adolescents over 15 years of age, who are also receiving medical, social and psychological support.

2. What you need to know before you take Suboxone

Do not take Suboxone
- if you are allergic (hypersensitive) to buprenorphine, naloxone or any of the other ingredients of this medicine (see section 6)
- if you have **serious breathing problems**
- if you have **serious liver problems**
- if you are intoxicated due to alcohol or have trembling, sweating, anxiety, confusion, or hallucinations caused by alcohol.
- if you are taking naltrexone or nalmefene for the treatment of alcohol or opioid dependence.

Warnings and precautions

Talk to your doctor before taking Suboxone if you have:
- asthma or other breathing problems
- any liver disease such as hepatitis
- low blood pressure
- recently suffered a head injury or brain disease
- a urinary disorder (especially linked to enlarged prostrate in men)
- any kidney disease
- thyroid problems
- adrenocortical disorder (e.g. Addison’s disease)

Important things to be aware of:

- **Additional monitoring**
  You may be more closely monitored by your doctor if you are below the age of 18 or over the age of 65. This medicine should not be taken by those under 15 years of age.

- **Misuse and abuse**
  This medicine can be a target for people who abuse prescription medicines, and should be kept in a safe place to protect it from theft. **Do not give this medicine to anyone else**. It can cause death or otherwise harm them.

- **Breathing problems**
  Some people have died from respiratory failure (inability to breathe) because they misused this medicine or took it in combination with other central nervous system depressants, such as alcohol, benzodiazepines (tranquilisers), or other opioids.

  This medicine may cause severe, possibly fatal, respiratory depression (reduced ability to breathe) in children and non-dependent people who accidentally or deliberately take it.

- **Dependence**
  This product can cause dependence.

- **Withdrawal symptoms**
  This product can cause withdrawal symptoms if you take it less than six hours after you use a short-acting opioid (e.g. morphine, heroin) or less than 24 hours after you use a long-acting opioid such as methadone.

  Suboxone can also cause withdrawal symptoms if you stop taking it abruptly.

- **Liver damage**
  Liver damage has been reported after taking Suboxone, especially when the medicine is misused. This could also be due to viral infections (chronic hepatitis C), alcohol abuse, anorexia or use of other medicines with the ability to harm your liver (see section 4). **Regular blood tests may be conducted by your doctor to monitor the condition of your liver. Tell your doctor if you have any liver problems before you start treatment with Suboxone.**

- **Blood pressure**
  This product may cause your blood pressure to drop suddenly, causing you to feel dizzy if you get up too quickly from sitting or lying down.

- **Diagnosis of unrelated medical conditions**
  This medicine may mask pain symptoms that could assist in the diagnosis of some diseases. Do not forget to advise your doctor if you take this medicine.

Other medicines and Suboxone
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Some medicines may increase the side effects of Suboxone and may sometimes cause very serious reactions. Do not take any other medicines whilst taking Suboxone without first talking to your doctor, especially:

- **Benzodiazepines** (used to treat anxiety or sleep disorders) such as diazepam, temazepam, alprazolam. Your doctor will prescribe the correct dose for you. **Taking the wrong dose of benzodiazepines may cause death due to respiratory failure (inability to breathe).**

- **Other medicines that may make you feel sleepy which are** used to treat illnesses such as anxiety, sleeplessness, convulsions/seizures, pain. These types of medicines will reduce you alertness levels making it difficult for you to drive and use machines. They may also cause central nervous system depression, which is very serious. Below is a list of examples of these types of medicines:

- other opioid containing medicines such as methadone, certain pain killers and cough suppressants
- anti-depressants (used to treat depression) such as isocarboxazid, phenelzine, selegiline, tranylcypromine and valproate may increase the effects of this medicine.
- sedative H1 receptor antagonists (used to treat allergic reactions) such as diphenhydramine and chlorphenamine.
- barbiturates (used to cause sleep or sedation) such as Phenobarbital, secobarbital
- tranquilisers (used to cause sleep or sedation) such as chloral hydrate.

- clonidine (used to treat high blood pressure) may extend the effects of this medicine.
- anti-retrovirals (used to treat HIV) such as ritonavir, nelfinavir, indinavir may increase the effects of this medicine.
- some antifungal agents (used to treat fungal infections) such as ketoconazole, itraconazole, certain antibiotics, may extend the effects of this medicine.
- some medicines may decrease the effect of Suboxone. These include medicines used to treat epilepsy (such as carbamazepine and phenytoin), and medicines used to treat tuberculosis (rifampicin).
- naltrexone and nalmefene (drugs used to treat addiction disorders) may prevent the therapeutic effects of Suboxone. They should not be taken at the same time as Suboxone treatment because you may experience a sudden onset of prolonged and intense withdrawal.

Suboxone with food, drink and alcohol
Alcohol may increase drowsiness and may increase the risk of respiratory failure if taken with Suboxone. **Do not take Suboxone together with alcohol.** Do not swallow or consume food or any drink until the tablet is completely dissolved.

Pregnancy and breast-feeding
The risks of using Suboxone in pregnant women are not known. Tell your doctor if you are pregnant or intend to become pregnant. Your doctor will decide if your treatment should be continued with an alternative medicine.

When taken during pregnancy, particularly late pregnancy, medicines like Suboxone may cause drug withdrawal symptoms including problems with breathing in your newborn baby. This may appear several days after birth.

Do not breast-feed whilst taking this medicine, since Suboxone passes into breast milk.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Suboxone may cause drowsiness. This may happen more often in the first few weeks of treatment when your dose is being changed, but can also happen if you drink alcohol or take other sedative medicines when you take Suboxone. Do not drive, use any tools or machines, or perform dangerous activities until you know how this medicine affects you.

Suboxone contains lactose
If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Suboxone

Your treatment is prescribed and monitored by doctors who are experienced in the treatment of drug dependence.

Your doctor will determine the best dose for you. During your treatment, the doctor may adjust the dose, depending upon your response.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Starting treatment

The recommended starting dose for adults and adolescents over the age of 15 years is one to two tablets of Suboxone 2 mg/0.5 mg. An additional one to two tablets of the Suboxone 2 mg/0.5 mg may be administered on day 1 depending on your needs.

Clear signs of withdrawal should be evident before taking your first dose of Suboxone. A doctor's assessment of your readiness for treatment will guide the timing of your first Suboxone dose.

- Starting treatment of Suboxone whilst dependent on heroin

  If you are dependent upon heroin or a short acting opioid, your first dose of Suboxone should be taken when signs of withdrawal appear, but not less than 6 hours after you last used opioids.

- Starting treatment of Suboxone whilst dependent on methadone

  If you have been taking methadone or a long acting opioid, the dose of methadone should ideally be reduced to below 30 mg/day before beginning Suboxone therapy. The first dose of Suboxone should be taken when signs of withdrawal appear, but not less than 24 hours after you last used methadone.

Taking Suboxone

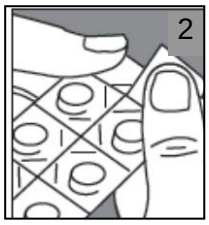
- Take the dose once a day by placing the tablets under the tongue.

- Keep the tablets in place under the tongue until they have **completely dissolved**. This may take 5-10 minutes.

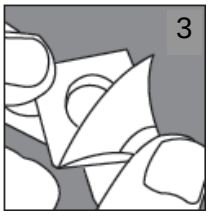
- Do not chew or swallow the tablets, as the medicine will not work and you may get withdrawal symptoms.

Do not consume any food or drink until the tablets have completely dissolved
How to remove the tablet from the blister

1 - Do not push the tablet through the foil.



2 - Remove just one section from the blister pack, tearing it along the perforated line.



3 – Starting from the edge where the seal is lifted, pull back the foil on the back to remove the tablet.

If the blister is damaged, discard the tablet.

Dosage adjustment and maintenance therapy:

During the days after you start treatment, your doctor may increase the dose of Suboxone you take according to your needs. If you have the impression that the effect of Suboxone is too strong or too weak, talk to your doctor or pharmacist, The maximum daily dose is 24 mg.

After a time of successful treatment, you may agree with your doctor to reduce the dose gradually to a lower maintenance dose.

Stopping treatment

Depending on your condition, the dose of Suboxone may continue to be reduced under careful medical supervision, until eventually it may be stopped.

Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you.

If you take more Suboxone than you should
If you or someone else takes too much of this medicine, you must go or be taken immediately to an emergency centre or hospital for treatment as **overdose** with Suboxone may cause serious and life-threatening breathing problems.
Symptoms of overdose may include feeling sleepy and uncoordinated with slowed reflexes, blurred vision, and/or slurred speech. You may be unable to think clearly, and may breathe much slower than is normal for you.

If you forget to take Suboxone
Tell your doctor as soon as possible if you miss a dose.

If you stop taking Suboxone

Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you. **Stopping treatment suddenly may cause withdrawal symptoms.**

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Suboxone can cause side effects, although not everybody gets them.

Tell your doctor immediately or seek urgent medical attention if you experience side effects, such as:

- swelling of the face, lips, tongue or throat which may cause difficulty in swallowing or breathing, severe hives/nettle rash. These may be signs of a life-threatening allergic reaction.
- feeling sleepy and uncoordinated, have blurred vision, have slurred speech, cannot think well or clearly, or your breathing gets much slower than is normal for you.

Also tell your doctor immediately if you experience side effects such as:

- severe tiredness, itching with yellowing of skin or eyes. These may be symptoms of liver damage.
- seeing or hearing things that are not there (hallucinations).

Side effects reported with Suboxone
Very common side effects (may effect more than one in 10 people):
Insomnia (inability to sleep), constipation, nausea, excessive sweating, headache, drug withdrawal syndrome
Common side effects (may effect up to 1 in 10 people):
Weight loss, swelling (hands and feet), drowsiness, anxiety, nervousness, tingling, depression, decreased sexual drive, increase in muscle tension, abnormal thinking, increased tearing (watering eyes) or other tearing disorder, blurred vision, flushing, increased blood pressure, migraines, runny nose, sore throat and painful swallowing, increased cough, upset stomach or other stomach discomfort, diarrhoea, abnormal liver function, flatulence, vomiting, rash, itching, hives, pain, joint pain, muscle pain, leg cramps (muscle spasm), difficulty in getting or keeping an erection, urine abnormality, abdominal pain, back pain, weakness, infection, chills, chest pain, fever, flu-like symptoms, feeling of general discomfort, accidental injury caused by loss of alertness or co-ordination, faintness and dizziness.
Uncommon side effects (may effect up to 1 in 100 people):
Swollen glands (lymph nodes), agitation, tremor, abnormal dream, excessive muscle activity, depersonalisation (not feeling like yourself), medicine dependence, amnesia (memory disturbance), loss of interest, exaggerated feeling of well-being, convulsion (fits), speech disorder, small pupil size, difficulty urinating, eye inflammation or infection, rapid or slow heartbeat, low blood pressure, palpitations, myocardial infarction (heart attack), chest tightness, shortness of breath, asthma, yawning, pain and sores in mouth, tongue discolouration, acne, skin nodule, hair loss, dry or scaling skin, inflammation of joints, urinary tract infection, abnormal blood tests, blood in urine, abnormal ejaculation, menstrual or vaginal problems, kidney stone, protein in your urine, painful or difficult urination, sensitivity to heat or cold, heat stroke, loss of appetite, feelings of hostility.
Not known (frequency cannot be estimated from the available data):
Sudden withdrawal syndrome caused by taking Suboxone too soon after use of illicit opioids, drug withdrawal syndrome in newborn. Slow or difficult breathing, liver injury with or without jaundice, hallucinations, swelling of face and throat or life threatening allergic reactions, drop

in blood pressure on changing position from sitting or lying down to standing.
Misusing this medicine by injecting it can cause withdrawal symptoms, infections, other skin reactions and potentially serious liver problems (see Warnings and precautions).

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Suboxone

Keep out of the sight and reach of children and other household members.

Do not use the medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month

This medicinal product does not require any special storage conditions. However, Suboxone can be a target for people who abuse prescription medicine. Keep this medicine in a safe place to protect it from theft.

Store the blister safely.
Never open the blister in advance.
Do not take this medicine in front of children.
An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Content of the pack and other Information

What Suboxone contains

- The active substances are buprenorphine and naloxone.
  Each 16 mg/4 mg sublingual tablet contains 16 mg buprenorphine (as hydrochloride) and 4 mg naloxone (as hydrochloride dihydrate).
- The other ingredients are lactose monohydrate, mannitol, maize starch, povidone K30, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium and natural lemon and lime flavour.

What Suboxone looks like and contents of the pack

Suboxone 16 mg/4 mg sublingual tablets are white round biconvex tablets of 10.5 mm with "N16" debossed on one side.
Packed in packs of 7 and 28 tablets.
Not all pack sizes may be marketed.

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Manufacturer
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For any information about this medicine, please contact the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the website of the European Medicines Agency http://www.ema.europa.eu/