ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 2 mg/0.5 mg sublingual tablets
Suboxone 8 mg/2 mg sublingual tablets
Suboxone 16 mg/4 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Suboxone 2 mg/0.5 mg sublingual tablets
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.

Suboxone 8 mg/2 mg sublingual tablets
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.

Suboxone 16 mg/4 mg sublingual tablets
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

Suboxone 2 mg/0.5 mg sublingual tablets
White hexagonal biconvex tablets of 6.5 mm with “N2” debossed on one side.

Suboxone 8 mg/2 mg sublingual tablets
White hexagonal biconvex tablets of 11 mm with “N8” debossed on one side.

Suboxone 16 mg/4 mg sublingual tablets
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. Suboxone is indicated 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 must 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 must 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 4 mg/1 mg and can be repeated up to a maximum dose of 12 mg/ 3 mg on day 1 to minimise undue withdrawal symptoms and retain the patient in treatment.
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 stabilisation and maintenance therapy
Following treatment induction on day 1, the patient must be rapidly stabilised on an adequate maintenance dose by titrating to achieve a dose that holds the patient in treatment and suppresses opioid withdrawal effects and is guided by reassessment of the clinical and psychological status of the patient. The maximum single daily dose should not exceed 24 mg buprenorphine.

During maintenance therapy, it may be necessary to periodically restabilise the patient on a new maintenance dose in response to changing patient needs.

Less than daily dosing
After a satisfactory stabilisation has been achieved the frequency of Suboxone 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/2 mg may be given 16 mg/4 mg on alternate days, with no dose on the intervening days. In some patients, after a satisfactory stabilisation has been achieved, the frequency of Suboxone dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no dose on the intervening days. However, the dose given on any one day should not exceed 24 mg . Patients requiring a titrated daily dose> 8 mg /day may not find this regimen adequate.

Medical withdrawal
After a satisfactory stabilisation has been achieved, if the patient agrees, the dose may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of the sublingual tablet in doses of 2 mg/0.5 mg and 8 mg/2 mg allows for a downward

titration of dose. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg sublingual tablet may be used. Patients should be monitored following medical withdrawal because of the potential for relapse.

Switching between buprenorphine and buprenorphine/naloxone
When used sublingually, buprenorphine/naloxone and buprenorphine have similar clinical effects and are interchangeable; however, before switching between buprenorphine/naloxone and buprenorphine, the prescriber and patient should agree to the change, and the patient should be monitored in case a need to readjust the dose occurs.

Switching between sublingual tablet and film (where applicable)
Patients being switched between Suboxone sublingual tablets and Suboxone film should be started on the same dose as the previously administered medicinal product. However, dose adjustments may be necessary when switching between medicinal products. Due to the potentially greater relative bioavailability of Suboxone film compared to Suboxone sublingual tablets, patients switching from sublingual tablets to film should be monitored for overdose. Those switching from film to sublingual tablets should be monitored for withdrawal or other indications of underdosing. In clinical studies, the pharmacokinetics of Suboxone film were not consistently shown to be similar to the respective dosage strengths of Suboxone sublingual tablets, as well as to the combinations (see section 5.2). If switching between Suboxone film and Suboxone sublingual tablets, the patient should be monitored in case a need to readjust the dose occurs. Combining different formulations or alternating between film and sublingual tablet formulations is not advised.

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
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 sections 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 sections 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 medicinal product is distributed for illicit use directly by the intended patient or if it is not safeguarded against theft.

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

To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing buprenorphine, such as avoiding prescribing multiple refills early in treatment, and conducting patient follow-up visits with clinical monitoring that is appropriate for 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 with buprenorphine alone since the naloxone in this medicinal product can precipitate withdrawal in individual’s dependent on heroin, methadone, or other opioid agonists.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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 the 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 medicinal 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 medicinal product 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 benzodiazepines, tranquilisers, sedatives or hypnotics see sections 4.5 and 4.7).

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products
Concomitant use of buprenorphine/naloxone and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe buprenorphine/naloxone concomitantly with sedative medicinal products, the lowest effective dose of the sedative medicines should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Serotonin syndrome
Concomitant administration of Suboxone and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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 medicinal product) 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 aetiological 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 effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Both buprenorphine and naloxone are extensively metabolised in the liver, and plasma levels were found to behigher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment compared with healthy subjects. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine.

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 greater risk of liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Buprenorphine/naloxone should be used with caution in patients with moderate hepatic impairment (see sections 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).

CYP 3A4 inhibitors
Medicinal products 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).

Class effects
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, in other circumstances where cerebrospinal pressure may be increased, or in patients with a 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).

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Paediatric population

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.

4.5 Interaction with other medicinal products and other forms of interaction

Buprenorphine/naloxone should not be taken together with:

- Alcoholic drinks or medicinal products containing alcohol, as alcohol increases the sedative effect of buprenorphine (see section 4.7).

Suboxone should be used cautiously when co-administered with:

- Sedatives such as benzodiazepines or related medicinal products
  The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use of sedative medicinal products should be limited (see section 4.4). Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this medicinal product and should also be cautioned to use benzodiazepines concurrently with this medicinal 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 H1-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.

- Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitor (SNRIs) or tricyclic

antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

- 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 Cmax 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 or limited amount of data from the use of buprenorphine/naloxone 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 fetus.

Breast-feeding
It is unknown whether naloxone is excreted in human milk. Buprenorphine and its metabolites are excreted in human milk. In rat's 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 medicinal 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 adversely 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 studies 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 undesirable 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	Abnormal dreams Agitation Apathy Depersonalisation	Hallucination

System Organ Class	Very common	Common	Uncommon	Not known
		Thinking abnormal	Drug dependence Euphoric mood Hostility	
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 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		Erectile	Amenorrhoea	

System Organ Class	Very common	Common	Uncommon	Not known
system and breast disorders		dysfunction	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
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 reactions 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 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. 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 and safety

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 versus 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 increasing 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.

Table 2: Buprenorphine Mean Pharmacokinetic Parameters

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)

Table 3. Changes in pharmacokinetic parameters for Suboxone film administered sublingually or buccally in comparison to Suboxone sublingual tablet

Dosage	PK Parameter	**Increase in Buprenorphine**			PK Parameter	**Increase in Naloxone**		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 × 2 mg/0.5 mg	C_{max}	22 %	25 %	-	C_{max}	-	-	-
	AUC_{0-last}	-	19 %	-	AUC_{0-last}	-	-	-
2 × 2 mg/0.5 mg	C_{max}	-	21 %	21 %	C_{max}	-	17 %	21 %
	AUC_{0-last}	-	23 %	16 %	AUC_{0-last}	-	22 %	24 %
1 × 8 mg/2 mg	C_{max}	28 %	34 %	-	C_{max}	41 %	54 %	-
	AUC_{0-last}	20 %	25 %	-	AUC_{0-last}	30 %	43 %	-
1 × 12 mg/3 mg	C_{max}	37 %	47 %	-	C_{max}	57 %	72 %	9 %
	AUC_{0-last}	21 %	29 %	-	AUC_{0-last}	45 %	57 %	-
1 × 8 mg/2 mg plus 2 × 2 mg/0.5 mg	C_{max}	-	27 %	13 %	C_{max}	17 %	38 %	19 %
	AUC_{0-last}	-	23 %	-	AUC_{0-last}	-	30 %	19 %

Note 1. '– 'represents no change when the 90 % confidence intervals for the geometric mean ratios of the C_{max} and $AUC_{0\text{-}last}$ values are within the 80 % to 125 % limit.
Note 2. There are no data for the 4 mg/1 mg strength film; it is compositionally proportional to the 2 mg/0.5 mg strength film and has the same size as the 2 × 2 mg/0.5 mg film strength.

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

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

Biotransformation
Buprenorphine is primarily metabolised through N-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation. Norbuprenorphine binds to opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of buprenorphine/naloxone.

Elimination
Elimination of buprenorphine is bi- or tri-exponential, and has a mean half-life from plasma of 32 hours.
Buprenorphine is excreted in the faeces (~70 %) by biliary excretion of the glucuroconjugated metabolites, the rest (~30 %) being excreted in the urine.

Linearity/non-linearity
Buprenorphine C_{max} and AUC increased in a linear fashion with the increasing dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

<u>Naloxone</u>

Absorption and distribution
Following sublingual administration of buprenorphine/naloxone, plasma naloxone concentrations are low and decline rapidly. Naloxone mean peak plasma concentrations were too low to assess dose-proportionality.
Naloxone has not been found to affect the pharmacokinetics of buprenorphine, and both buprenorphine sublingual tablets and buprenorphine/naloxone sublingual film deliver similar plasma concentrations of buprenorphine.

Distribution
Naloxone is approximately 45 % protein bound, primarily to albumin.

Biotransformation
Naloxone is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as N-dealkylation and reduction of the 6-oxo group.

Elimination
Naloxone is excreted in the urine, with a mean half-life of elimination from plasma ranging from 0.9 to 9 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 4 summarises the results from a clinical trial in which the exposure of buprenorphine and naloxone was determined after administering a buprenorphine/naloxone 2.0/0.5 mg sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 4. 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 agonist 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/naloxone 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 mg/kg/day, 30 mg/kg/day and 120 mg/kg/day, with estimated exposure multiples of 3 times 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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Suboxone 2 mg/0.5 mg sublingual tablets
EU/1/06/359/001
EU/1/06/359/002

Suboxone 8 mg/2 mg sublingual tablets
EU/1/06/359/003
EU/1/06/359/004

Suboxone 16 mg/4 mg sublingual tablets
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: 16 September 2011

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 2 mg/0.5 mg sublingual film
Suboxone 4 mg/1 mg sublingual film
Suboxone 8 mg/2 mg sublingual film
Suboxone 12 mg/3 mg sublingual film

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Suboxone 2 mg/0.5 mg sublingual film
Each film contains 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate).
Excipients with known effect
Each film contains 5.87 mg maltitol liquid and 0.01 mg sunset yellow (E 110).

Suboxone 4 mg/1 mg sublingual film
Each film contains 4 mg buprenorphine (as hydrochloride) and 1 mg naloxone (as hydrochloride dihydrate).
Excipients with known effect
Each film contains 11.74 mg maltitol liquid and 0.02 mg sunset yellow (E 110).

Suboxone 8 mg/2 mg sublingual film
Each film contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate).
Excipients with known effect
Each film contains 6.02 mg maltitol liquid and 0.02 mg sunset yellow (E 110).

Suboxone 12 mg/3 mg sublingual film
Each film contains 12 mg buprenorphine (as hydrochloride) and 3 mg naloxone (as hydrochloride dihydrate).
Excipients with known effect
Each film contains 9.03 mg maltitol liquid and 0.02 mg sunset yellow (E 110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual film

Suboxone 2 mg/0.5 mg sublingual film
2 mg/0.5 mg orange rectangular film of nominal dimensions 22.0 mm × 12.8 mm, with ‘N2’ imprinted in white ink.

Suboxone 4 mg/1 mg sublingual film
4 mg/1 mg orange rectangular film of nominal dimensions 22.0 mm × 25.6 mm, with ‘N4’ imprinted in white ink.

Suboxone 8 mg/2 mg sublingual film
8 mg/2 mg orange rectangular film of nominal dimensions 22.0 mm × 12.8 mm, with ‘N8’ imprinted in white ink.

Suboxone 12 mg/3 mg sublingual film
12 mg/3 mg orange rectangular film of nominal dimensions 22.0 mm × 19.2 mm, with 'N12' imprinted in white ink.

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. Suboxone is indicated 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 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 must 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 must 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 4 mg/1 mg and can be repeated up to a maximum dose of 12 mg/ 3 mg on day 1 to minimise undue withdrawal symptoms and retain the patient in treatment.

Due to naloxone exposure being somewhat higher following buccal administration than sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimise naloxone exposure and to reduce the risk of precipitated withdrawal.

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 stabilisation and maintenance therapy
Following treatment induction on day 1, the patient must be rapidly stabilised on an adequate maintenance dose by titrating to achieve a dose that holds the patient in treatment and suppresses opioid withdrawal effects and is guided by reassessment of the clinical and psychological status of the patient. The maximum single daily dose should not exceed 24 mg buprenorphine.

During maintenance therapy, it may be necessary to periodically restabilise the patient on a new maintenance dose in response to changing patient needs.

Less than daily dosing
After a satisfactory stabilisation has been achieved the frequency of Suboxone 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/2 mg may be given 16 mg/4 mg on alternate days, with no dose on the intervening days. In some patients, after a satisfactory stabilisation has been achieved, the frequency of Suboxone dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no dose on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.

Medical withdrawal
After a satisfactory stabilisation has been achieved, if the patient agrees, the dose may be reduced gradually to a lower maintenance dose, in some favourable cases, treatment may be discontinued. The availability of the sublingual film in doses of 2 mg/0.5 mg, 4 mg/1 mg and 8 mg/2 mg allows for a downward titration of dose. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg sublingual tablets may be used. Patients should be monitored following medical withdrawal because of the potential for relapse.

Switching between sublingual and buccal sites of administration
The systemic exposure of buprenorphine between buccal and sublingual administration of Suboxone film is approximately similar (see section 5.2). Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under- or overdosing.

Switching between buprenorphine and buprenorphine/naloxone
When used sublingually, buprenorphine/naloxone and buprenorphine have similar clinical effects and are interchangeable; however, before switching between buprenorphine/naloxone and buprenorphine, the prescriber and patient should agree to the change, and the patient should be monitored in case a need to readjust the dose occurs.

Switching between sublingual tablet and film (where applicable)
Patients being switched between Suboxone sublingual tablets and Suboxone film should be started on the same dose as the previously administered medicinal product. However, dose adjustments may be necessary when switching between medicinal products. Due to the potentially greater relative bioavailability of Suboxone film compared to Suboxone sublingual tablets, patients switching from sublingual tablets to film should be monitored for overdose. Those switching from film to sublingual tablets should be monitored for withdrawal or other indications of underdosing. In clinical studies, the pharmacokinetics of Suboxone film were not consistently shown to be similar to the respective dosage strengths of Suboxone sublingual tablets, as well as to the combinations (see section 5.2). If switching between Suboxone film and Suboxone sublingual tablets, the patient should be monitored in case a need to readjust the dose occurs. Combining different formulations or alternating between film and sublingual tablet formulations is not advised.

Special populations

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

Hepatic impairment
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 sections 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 sections 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

Sublingual use and/or buccal use only.

For induction buprenorphine/naloxone should be administered sublingually. For maintenance therapy, Suboxone film may be administered buccally and/or sublingually.

The film is not to be swallowed. The film is to be placed under the tongue or inside either cheek until completely dissolved. It is advised that patients moisten their mouths prior to dosing. Patients should not swallow or consume food or drink until the film is completely dissolved. The film should not be moved after placement, and proper administration technique should be demonstrated to the patient.

For buccal use one film should be placed on the inside of the right or left cheek. If an additional film is necessary to achieve the prescribed dose, an additional film should be placed on the opposite side. The film must be kept on the inside of the cheek until completely dissolved. If a third film is necessary to achieve the prescribed dose, it should be placed on the inside of the right or left cheek after the first two films have dissolved.

For sublingual use one film should be placed under the tongue. If an additional film is necessary to achieve the prescribed dose, an additional film should be placed under the tongue on the opposite side. The film must be kept under the tongue until completely dissolved. If a third film is necessary to achieve the prescribed dose, it should be placed under the tongue after the first two films have dissolved.

A daily dose can be made up from multiple Suboxone films of different strengths. This may be taken all at the same time or in two divided portions. The second portion should be placed sublingually and/or buccally directly after the first portion has dissolved.

No more than two films should be administered at the same time. It should be ensured that the films do not overlap.

The film is not designed to be split or subdivided into smaller doses.

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 medicinal product is distributed for illicit use directly by the intended patient or if it is not safeguarded against theft.

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

To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing buprenorphine, such as avoiding prescribing multiple refills early in treatment, and conducting patient follow-up visits with clinical monitoring that is appropriate for 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 with buprenorphine alone since the naloxone in this medicinal product can precipitate withdrawal in individual's dependent on heroin, methadone, or other opioid agonists.

Sleep-related breathing disorders

Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

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 the 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 medicinal 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 sachet safely, to never open the sachet in advance, to keep them out of the reach of children and other household members, and not to use this medicinal product 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 benzodiazepines, tranquilisers, sedatives or hypnotics; see sections 4.5 and 4.7).

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products

Concomitant use of buprenorphine/naloxone and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe buprenorphine/naloxone concomitantly with sedative medicinal products, the lowest effective dose of the sedative medicines should be used, and the duration of treatment should be as short as possible. The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Serotonin syndrome

Concomitant administration of Suboxone and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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 medicinal products) 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 aetiological 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 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 effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Both buprenorphine and naloxone are extensively metabolised in the liver, and plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment compared with healthy subjects. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine.

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 greater risk of liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Buprenorphine/naloxone should be used with caution in patients with moderate hepatic impairment (see sections 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).

CYP3 A4 inhibitors

Medicinal products 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).

Class effects

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, in other circumstances where cerebrospinal pressure may be increased, or in patients with a 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).

Excipients

This medicinal product contains maltitol liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.
This medicinal product contains sunset yellow (E 110). Sunset yellow may cause allergic reactions.
This medicinal product contains less than 1 mmol sodium (23 mg) per film i.e. essentially “sodium free”.

Paediatric population

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.

4.5 Interaction with other medicinal products and other forms of interaction

Buprenorphine/naloxone should not be taken together with:

- Alcoholic drinks or medicinal products containing alcohol, as alcohol increases the sedative effect of buprenorphine (see section 4.7).

Buprenorphine/naloxone should be used cautiously when co-administered with:

- Sedatives such as benzodiazepines or related medicinal products
  The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use of sedative medicinal products should be limited (see section 4.4). Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this medicinal product and should also be cautioned to use benzodiazepines concurrently with this medicinal 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 H1-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.

- Serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitor (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

- 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 MAOI might produce exaggeration of the effects of opioids, based on experience with morphine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of buprenorphine/naloxone 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 fetus.

Breast-feeding

It is unknown whether naloxone is excreted in human milk. Buprenorphine and its metabolites are excreted in human milk. In rat's 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 medicinal 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 adversely 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 studies 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.

The most commonly reported treatment-related adverse reactions associated with the sublingual or buccal administration of buprenorphine/naloxone were oral hypoesthesia and oral mucosal erythema, respectively. Other treatment-related adverse reactions reported by more than one patient were constipation, glossodynia and vomiting.

Tabulated list of adverse reactions

Adverse reactions reported during post-marketing surveillance are also included.

The frequency of possible undesirable 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 the 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	

System Organ Class	Very common	Common	Uncommon	Not Known
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, Disturbance in attention, Hyperkinesia, Seizure, Speech disorder, Tremor	Hepatic encephalopathy, Syncope
Eye disorders		Amblyopia, Lacrimal disorder	Conjunctivitis, Miosis, Vision blurred	
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, Oral mucosal erythema, Vomiting	Hypoaesthesia oral, Glossodynia, Mouth ulceration, Oedema mouth, Oral pain, Paraesthesia oral, Tongue discolouration	Glossitis, Stomatitis
Hepatobiliary disorders		Hepatic function abnormal		Hepatitis, Hepatitis acute, Jaundice,

System Organ Class	Very common	Common	Uncommon	Not Known
				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
Investigations		Liver function test abnormal, Weight decreased	Blood creatinine increased	Transaminases increased
Injury, poisoning and procedural complications		Injury	Heat stroke, Poisoning (Intoxication)	

Description of selected adverse reactions

In cases of intravenous drug misuse, some adverse reactions 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 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. 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 and safety

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 versus 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.

In a multicentre RCT study, 92 patients received either Suboxone film or Suboxone sublingual tablets following a 7-day run-in period with Suboxone sublingual tablets. It took 4 minutes on average for the sublingual tablets to visibly dissolve and 3 minutes on average for the sublingual film to dissolve. As concerns removability of sublingually applied films it was demonstrated that after 30 seconds of the application of a single film, none of the study participants could remove some or all the film. However, when 2 or more films were administered the participants were more likely to be able to remove some or all the film after 30 seconds. No more than 2 films should be administered at the same time (see section 4.2).

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.

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

Table 2. Pharmacokinetic parameters (Mean ± SD) of buprenorphine and naloxone following sublingual administration of Suboxone film

PK Parameter	Suboxone film dose (mg)			
	2 mg/0.5 mg	**4 mg / 1 mg***	**8 mg / 2 mg**	**12 mg / 3 mg**
Buprenorphine				
C_{max} (ng/mL)	0.947 ± 0.374	1.40 ± 0.687	3.37 ± 1.80	4.55 ± 2.50
T_{max} (h) Median, (min-max)	1.53 (0.75 - 4.0)	1.50 (0.5, 3.0)	1.25 (0.75 - 4.0)	1.50 (0.5, 3.0)
AUC_{inf} (ng.hr/mL)	8.654 ± 2.854	13.71 ± 5.875	30.45 ± 13.03	42.06 ± 14.64
$t_{1/2}$ (hr)	33.41 ± 13.01	24.30 ± 11.03	32.82 ± 9.81	34.66 ± 9.16
Norbuprenorphine				
C_{max} (ng/mL)	0.312 ±0.140	0.617 ±0.311	1.40 ±1.08	2.37 ±1.87
T_{max} (h) Median, (min-max)	1.38 (0.5 - 8.0)	1.25 (0.5, 48.0)	1.25 (0.75 - 12.0)	1.25 (0.75, 8.0)
AUC_{inf} (ng.hr/mL)	14.52 ±5.776	23.73 ±10.60	54.91 ±36.01	71.77 ±29.38
$t_{1/2}$ (hr)	56.09 ±31.14	45.96 ±40.13	41.96 ±17.92	34.36 ±7.92
Naloxone				
C_{max} (ng/mL)	0.054 ± 0.023	0.0698 ± 0.0378	0.193 ± 0.091	0.238 ± 0.144
T_{max} (h) Median, (min-max)	0.75 (0.5 - 2.0)	0.75 (0.5, 1.5)	0.75 (0.5 - 1.25)	0.75 (0.50, 1.25)
AUC_{inf} (ng.hr/mL)	0.137 ± 0.043	0.204 ± 0.108	0.481 ± 0.201	0.653 ± 0.309
$t_{1/2}$ (hr)	5.00 ± 5.52	3.91 ± 3.37	6.25 ± 3.14	11.91 ± 13.80

*There are no data for the 4 mg/1 mg strength film; it is compositionally proportional to 2 mg/0.5 mg strength film and has the same size of 2 × 2 mg/0.5 mg film strength.

Table 3. Changes in pharmacokinetic parameters for Suboxone film administered sublingually or buccally in comparison to Suboxone sublingual tablet

Dosage	PK Parameter	**Increase in Buprenorphine**			PK Parameter	**Increase in Naloxone**		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 × 2 mg/0.5 mg	C_{max}	22 %	25 %	-	C_{max}	-	-	-
	$AUC_{0\text{-}last}$	-	19 %	-	$AUC_{0\text{-}last}$	-	-	-
2 × 2 mg/0.5 mg	C_{max}	-	21 %	21 %	C_{max}	-	17 %	21 %
	$AUC_{0\text{-}last}$	-	23 %	16 %	$AUC_{0\text{-}last}$	-	22 %	24 %
1 × 8 mg/2 mg	C_{max}	28 %	34 %	-	C_{max}	41 %	54 %	-
	$AUC_{0\text{-}last}$	20 %	25 %	-	$AUC_{0\text{-}last}$	30 %	43 %	-
1 × 12 mg/3 mg	C_{max}	37 %	47 %	-	C_{max}	57 %	72 %	9 %
	$AUC_{0\text{-}last}$	21 %	29 %	-	$AUC_{0\text{-}last}$	45 %	57 %	-
1 × 8 mg/2 mg plus 2 × 2 mg/0.5 mg	C_{max}	-	27 %	13 %	C_{max}	17 %	38 %	19 %
	$AUC_{0\text{-}last}$	-	23 %	-	$AUC_{0\text{-}last}$	-	30 %	19 %

Note 1. '– 'represents no change when the 90 % confidence intervals for the geometric mean ratios of the C_{max} and $AUC_{0\text{-}last}$ values are within the 80 % to 125 % limit.
Note 2. There are no data for the 4 mg/1 mg strength film; it is compositionally proportional to the 2 mg/0.5 mg strength film and has the same size as the 2 × 2 mg/0.5 mg film strength.

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

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

Biotransformation
Buprenorphine is primarily metabolised through N-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation. Norbuprenorphine binds to opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of buprenorphine/naloxone.

Elimination
Elimination of buprenorphine is bi- or tri-exponential, and the mean terminal elimination half-life from plasma is reported in Table 2.
Buprenorphine is excreted in the faeces (~70 %) by biliary excretion of the glucuroconjugated metabolites, the rest (~30 %) being excreted in the urine.

Linearity/non-linearity
Buprenorphine C_{max} and AUC increased in a linear fashion with the increasing dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

Naloxone

Absorption
Naloxone mean peak plasma concentrations were too low to assess dose-proportionality, and in seven of eight subjects tested who had naloxone plasma levels above the limit of quantification (0.05 ng/mL), naloxone was not detected beyond 2 hours post-dose.
Naloxone has not been found to affect the pharmacokinetics of buprenorphine, and both buprenorphine sublingual tablets and buprenorphine/naloxone sublingual film deliver similar plasma concentrations of buprenorphine.

Distribution
Naloxone is approximately 45 % protein bound, primarily to albumin.

Biotransformation
Naloxone is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as N-dealkylation and reduction of the 6-oxo group.

Elimination
Naloxone is excreted in the urine, with a mean half-life of elimination from plasma ranging from 2 to 12 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 were evaluated in a post-marketing study. Table 4 summarises the results from a clinical trial in which the exposure of buprenorphine and naloxone was determined after administering a buprenorphine/naloxone 2.0/0.5 mg sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 4. 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 agonist 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 1 × for buprenorphine and 5 × for naloxone at the maximum human therapeutic dose calculated on a mg/m^2 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/naloxone 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 2.4 × 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 mg/kg/day, 30 mg/kg/day and 120 mg/kg/day, with estimated exposure multiples of 3 times to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m^2 basis. Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol
Maltitol liquid
Natural lime flavour
Hypromellose
Citric acid
Acesulfame potassium
Sodium citrate
Sunset yellow (E 110)

Printing ink
Propylene Glycol (E1520)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

The films are packed in child-resistant individual sachets consisting of four composite layers of polyethylene terephthalate (PET), Low Density Polyethylene (LDPE), aluminium foil and Low-Density Polyethylene (LDPE), which are heat sealed at the edges.

Pack sizes: 7 × 1, 14 × 1 and 28 × 1 sublingual films.

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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Suboxone 2 mg/0.5 mg sublingual film
EU/1/06/359/007 7 × 1 sublingual film
EU/1/06/359/008 14 × 1 sublingual film
EU/1/06/359/009 28 × 1 sublingual film

Suboxone 4 mg/1 mg sublingual film
EU/1/06/359/010 7 × 1 sublingual film
EU/1/06/359/011 14 × 1 sublingual film
EU/1/06/359/012 28 × 1 sublingual film

Suboxone 8 mg/2 mg sublingual film
EU/1/06/359/013 7 × 1 sublingual film
EU/1/06/359/014 14 × 1 sublingual film
EU/1/06/359/015 28 × 1 sublingual film

Suboxone 12 mg/3 mg sublingual film
EU/1/06/359/016 7 × 1 sublingual film
EU/1/06/359/017 14 × 1 sublingual film
EU/1/06/359/018 28 × 1 sublingual film

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 16 September 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the web-site 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

Indivior Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 Europe 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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 Europe 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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

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 Europe Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 2 mg/0.5 mg sublingual film
buprenorphine/naloxone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains maltitol liquid and sunset yellow (E110)
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual film

7 × 1 sublingual film
14 × 1 sublingual film
28 × 1 sublingual film

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For sublingual use and/or buccal use only.
Do not swallow or chew.

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

Store below 25 °C

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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/007 (7 × 1 film)
EU/1/06/359/008 (14 × 1 film)
EU/1/06/359/009 (28 × 1 film)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Suboxone 2 mg/0.5 mg sublingual film

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Suboxone 2 mg/0.5 mg sublingual film
buprenorphine/naloxone

2. METHOD OF ADMINISTRATION

sublingual use and/or buccal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 sublingual film

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 4 mg/1 mg sublingual film
buprenorphine/naloxone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film contains 4 mg buprenorphine (as hydrochloride) and 1 mg naloxone (as hydrochloride dihydrate).

3. LIST OF EXCIPIENTS

Contains maltitol liquid and sunset yellow (E110)
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual film

7 × 1 sublingual film
14 × 1 sublingual film
28 × 1 sublingual film

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For sublingual use and/or buccal use only.
Do not swallow or chew.

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

Store below 25 °C

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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/010 (7 × 1 film)
EU/1/06/359/011 (14 × 1 film)
EU/1/06/359/012 (28 × 1 film)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Suboxone 4 mg/1 mg sublingual film

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Suboxone 4 mg/1 mg sublingual film
buprenorphine/naloxone

2. METHOD OF ADMINISTRATION

sublingual use and/or buccal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 sublingual film

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 8 mg/2 mg sublingual film
buprenorphine/naloxone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains maltitol liquid and sunset yellow (E 110)
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual film

7 × 1 sublingual film
14 × 1 sublingual film
28 × 1 sublingual film

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For sublingual use and/or buccal use only.
Do not swallow or chew.

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

Store below 25 °C

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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/013 (7 × 1 film)
EU/1/06/359/014 (14 × 1 film)
EU/1/06/359/015 (28 × 1 film)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Suboxone 8 mg/2 mg sublingual film

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Suboxone 8 mg/2 mg sublingual film
buprenorphine/naloxone

2. METHOD OF ADMINISTRATION

sublingual use and/or buccal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 sublingual film

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Suboxone 12 mg/3 mg sublingual film
buprenorphine/naloxone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film contains 12 mg buprenorphine (as hydrochloride) and 3 mg naloxone (as hydrochloride dihydrate).

3. LIST OF EXCIPIENTS

Contains maltitol liquid and sunset yellow (E 110)
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Sublingual film

7 × 1 sublingual film
14 × 1 sublingual film
28 × 1 sublingual film

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For sublingual use and/or buccal use only.
Do not swallow or chew.

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

Store below 25 °C

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 Europe Limited
27 Windsor Place
Dublin 2
D02 DK44
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/359/016 (7 × 1 film)
EU/1/06/359/017 (14 × 1 film)
EU/1/06/359/018 (28 × 1 film)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Suboxone 12 mg/3 mg sublingual film

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Suboxone 12 mg/3 mg sublingual film
buprenorphine/naloxone

2. METHOD OF ADMINISTRATION

sublingual use and/or buccal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 sublingual film

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Suboxone 2 mg/0.5 mg sublingual tablets
Suboxone 8 mg/2 mg sublingual tablets
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 or pharmacist. 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 to buprenorphine, naloxone or any of the other ingredients of this medicine (listed in section 6)
- if you have **serious breathing problems**
- if you have **serious problems with your liver**
- 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
- problems with your liver 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)
- depression or other conditions that are treated with antidepressants. The use of these medicines together with Suboxone can lead to serotonin syndrome, a potentially life-threatening condition (see ''Other medicines and Suboxone'').

Important things to be aware of:

- An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

- **Additional monitoring**
  You may be more closely monitored by your doctor if you are over the age of 65.

- **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 (see section 5). **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 buprenorphine or have taken 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.

- **Sleep-related breathing disorders**
  Suboxone can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

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

- **Withdrawal symptoms**
  This medicine can cause opioid withdrawal symptoms if you take it too soon after taking opioids. You should leave at least 6 hours after you use a short-acting opioid (e.g. morphine, heroin) or at least 24 hours after you use a long-acting opioid such as methadone.

  This medicine can also cause withdrawal symptoms if you stop taking it abruptly. See section 3 'stopping treatment'.

- **Liver damage**
  Liver damage has been reported after taking Suboxone, especially when the medicine is misused. This could also be due to viral infections (e.g. 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 medicine 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. You must tell your doctor that you take this medicine.

Children and adolescents
Do not give this medicine to **children under the age of 15**. If you are between 15 and 18 years old your doctor may monitor you more closely during treatment, because of the lack of data in this age group.

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, these can be serious. 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. Concomitant use of Suboxone and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor does prescribe Suboxone together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

- **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 may 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 painkillers and cough suppressants
- Antidepressants (used to treat depression) such as isocarboxazid, phenelzine, selegiline, tranylcypromine and valproate may increase the effects of this medicine.
- Sedative H_1 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.

- **Anti-depressants** such as moclobemide, tranylcypromine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine. These medicines may interact with Suboxone and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles, that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.

- 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 (medicines used to treat addictive 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
Do not have alcohol whilst being treated with this medicine. Alcohol may increase drowsiness and may increase the risk of respiratory failure if taken with Suboxone. Do not swallow or consume food or any drink until the tablet is completely dissolved.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. The risks of using Suboxone in pregnant women are not known. 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, as buprenorphine passes into breast milk.

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

Suboxone contains lactose and sodium.
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) tablet, that is to say essentially ‘sodium-free’.

3. How to take Suboxone

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

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 to treatment.

Starting treatment

The recommended starting dose for adults and adolescents over the age of 15 years is usually two Suboxone 2 mg/0.5 mg sublingual tablets.

This dose may be repeated to twice on day 1 depending on your needs.

You should be aware of the clear signs of withdrawal before taking your first dose of Suboxone. Your doctor will tell you when to take your first dose.

- Starting treatment of Suboxone whilst **dependent on heroin**

  If you are dependent upon heroin or a short acting opioid, your first dose should be taken when signs of withdrawal appear, **at least 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, and at **least 24 hours after you last used methadone.**

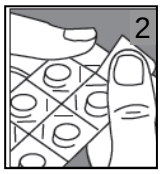
Taking Suboxone

- 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.

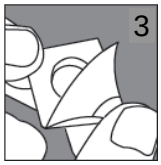
Do not consume any food or drink until the tablets have completely dissolved.

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

Dose 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 think that the effect of Suboxone is too strong or too weak, talk to your doctor or pharmacist. **The maximum daily dose is 24 mg buprenorphine**.

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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 affect more than one in 10 people):
Insomnia (inability to sleep), constipation, nausea, excessive sweating, headache, drug withdrawal syndrome
Common side effects (may affect up to 1 in 10 people):
Weight loss, swelling of the hands and feet, drowsiness, anxiety, nervousness, tingling, depression, decreased sexual drive, increase in muscle tension, abnormal thinking, increased tearing (watering eyes) or other tearing disorders, 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 affect 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 wellbeing, convulsion (fits), speech disorder, small pupil size, difficulty urinating, eye inflammation or infection, rapid or slow heartbeat, low blood pressure, palpitations, 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 new-born babies, 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 or pharmacist. 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 this medicine 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 medicine 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).
  Each 8 mg/2 mg sublingual tablet contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate).
  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 2 mg/0.5 mg sublingual tablets are white hexagonal biconvex tablets of 6.5 mm with “N2” debossed on one side.
Suboxone 8 mg/2 mg sublingual tablets are white hexagonal biconvex tablets of 11 mm with “N8” debossed on one side.
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.

Marketing Authorisation Holder and Manufacturer

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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 2 mg/0.5 mg sublingual film
Suboxone 4 mg/1 mg sublingual film
Suboxone 8 mg/2 mg sublingual film
Suboxone 12 mg/3 mg sublingual film

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 symptoms are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. 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 to opioid (narcotic) drugs such as heroin or morphine in patients 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** to **buprenorphine, naloxone** or any of the other ingredients of this medicine listed in section 6);
- if you have **serious breathing problems**;
- if you have **serious problems with your liver**;
- 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
- problems with your liver 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)
- depression or other conditions that are treated with antidepressants. The use of these medicines together with Suboxone can lead to serotonin syndrome, a potentially life-threatening condition (see ''Other medicines and Suboxone'').

Important things to be aware of:
- An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

- **Additional monitoring**
  You may be more closely monitored by your doctor if you are over the age of 65. .

- **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 (see section 5). **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 buprenorphine or have taken 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.

- **Sleep-related breathing disorders**
  Suboxone can cause sleep-related breathing disorders such as sleep apnoea (breathing pauses during sleep) and sleep related hypoxemia (low oxygen level in the blood). The symptoms can include breathing pauses during sleep, night awakening due to shortness of breath, difficulties to maintain sleep or excessive drowsiness during the day. If you or another person observe these symptoms, contact your doctor. A dose reduction may be considered by your doctor.

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

- **Withdrawal symptoms**
  This medicine can cause opioid withdrawal symptoms if you take it too soon after taking opioids. You should leave at least 6 hours after you use a short-acting opioid (e.g. morphine, heroin) or at least 24 hours after you use a long-acting opioid such as methadone.

  This medicine can also cause withdrawal symptoms if you stop taking it abruptly. See section 3 'stopping treatment'.

- **Liver damage**
  Liver damage has been reported after taking Suboxone, especially when the medicine is misused. This could also be due to viral infections (e.g. 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 medicine 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. You must tell your doctor that you take this medicine.

Children and adolescents
Do not give this medicine to **children under the age of 15**. If you are between 15 and 18 years old your doctor may monitor you more closely during treatment, because of the lack of data in this age group.

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 these can be serious. 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, or alprazolam**.** Concomitant use of Suboxone and sedative medicines such as benzodiazepines or related medicines increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible.
  However if your doctor does prescribe Suboxone together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor.
  Please tell your doctor about all sedative medicines you are taking, and follow your doctor's dose recommendation closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

- **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 may 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 painkillers and cough suppressants.
  - Antidepressants (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.

- **Anti-depressants** such as moclobemide, tranylcypromine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine. These medicines may interact with Suboxone and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles, that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.

- Clonidine (used to treat high blood pressure) may extend the effects of this medicine.

- Antiretrovirals (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 (medicines used to treat addictive 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
Do not have alcohol whilst being treated with this medicine. Alcohol may increase drowsiness and may increase the risk of respiratory failure if taken with Suboxone. Do not swallow or consume food or any drink until the film is completely dissolved.

Pregnancy, breast-feeding and fertility
Tell your doctor if you are pregnant, think you may be pregnant or are planning to have a baby. The risks of using Suboxone in pregnant women are not known. 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, as buprenorphine passes into breast milk.

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

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

Suboxone contains maltitol, sunset yellow (E110) and sodium.
Suboxone contains maltitol liquid. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

Suboxone contains sunset yellow (E110), which may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per film, that is to say essentially ‘sodium free’.

3. How to take Suboxone

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

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 to treatment.

Starting treatment
The recommended starting dose for adults and adolescents over the age of 15 years is usually two Suboxone 2 mg/0.5 mg sublingual films, or one Suboxone 4 mg/1 mg sublingual film.

This dose may be repeated up to twice on day 1 depending on your needs.

You should be aware of the clear signs of withdrawal before taking your first dose of Suboxone. Your doctor will tell you when to take your first dose.

- Starting treatment of Suboxone whilst **dependent on heroin**

  If you are dependent upon heroin or a short-acting opioid, your first dose should be taken when signs of withdrawal appear, **at least 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, and at **least 24 hours after you last used methadone**.

Dose 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 think that the effect of Suboxone is too strong or too weak, talk to your doctor or pharmacist. **The maximum daily dose is 24 mg buprenorphine.**

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

Taking Suboxone
- Take the dose once a day, at approximately the same time.
- It is advisable to moisten your mouth before taking the film.
- Place the sublingual film under the tongue (sublingual use) or on the inside of the cheek (buccal use) as advised by your doctor. Ensure the films do not overlap.
- Keep the films in place under the tongue, or inside of the cheek, until they have **completely dissolved**.
- **Do not chew or swallow** the film, as the medicine will not work, and you may get withdrawal symptoms.
- Do not consume any food or drink until the film has completely dissolved.
- Do not split the film or subdivide into smaller doses.

How to remove the film from the sachet

Each Suboxone film comes in a sealed child-resistant sachet. Do not open the sachet until you are ready to use it.

To open the sachet, find the dotted line that runs along the top edge of the sachet and fold the edge of the sachet along the dotted line (see Figure 1).

Figure 1

- Folding the sachet along the dotted line exposes a slit through the folded edge of the sachet that can then be torn in the direction of the arrow.

- Alternatively, the sachet may be cut with scissors along the arrow (see Figure 2).

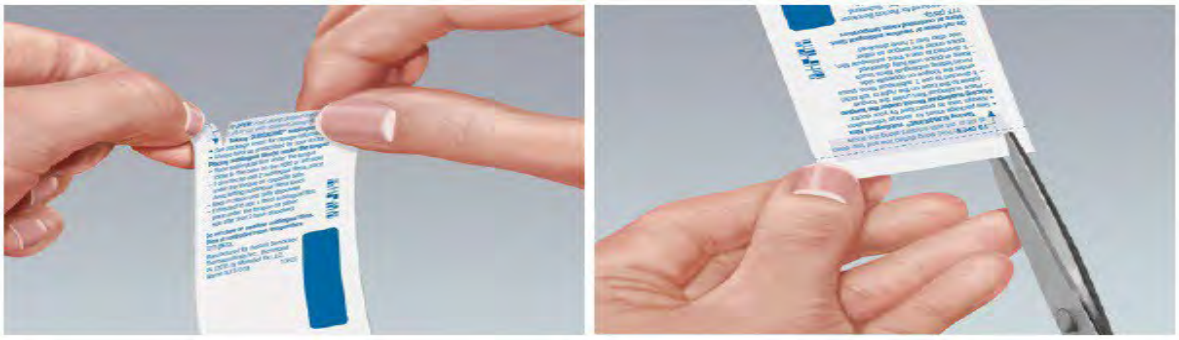

Figure 2

If the sachet is damaged, discard the film.

How to place a film under your tongue (sublingual use):
Drink water to moisten your mouth first. This helps the film dissolve more easily. Then, hold a film between two fingers by the outside edges, and place the film under your tongue, close to the base either to the left or right (see Figure 3).

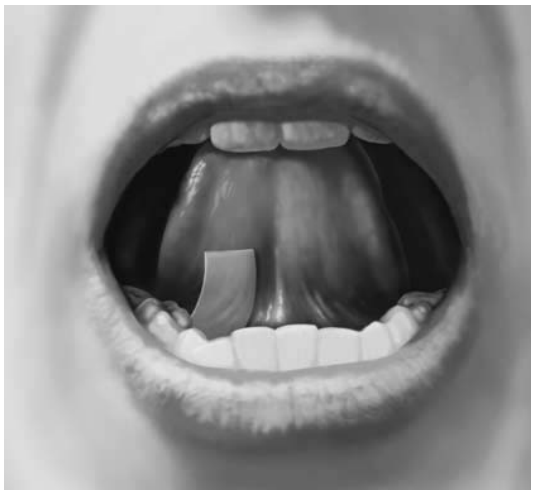

Figure 3

If your doctor tells you to take two films at a time, place the second film under your tongue on the

opposite side. Ensure the films do not overlap
If your doctor tells you to take a third film, place it under your tongue on either side after the first two films have dissolved.

How to place a film on the inside of your cheek (buccal use):
Drink water to moisten your mouth. Hold the film between two fingers by the outside edges and place one film on the inside of your right or left cheek (see Figure 4).

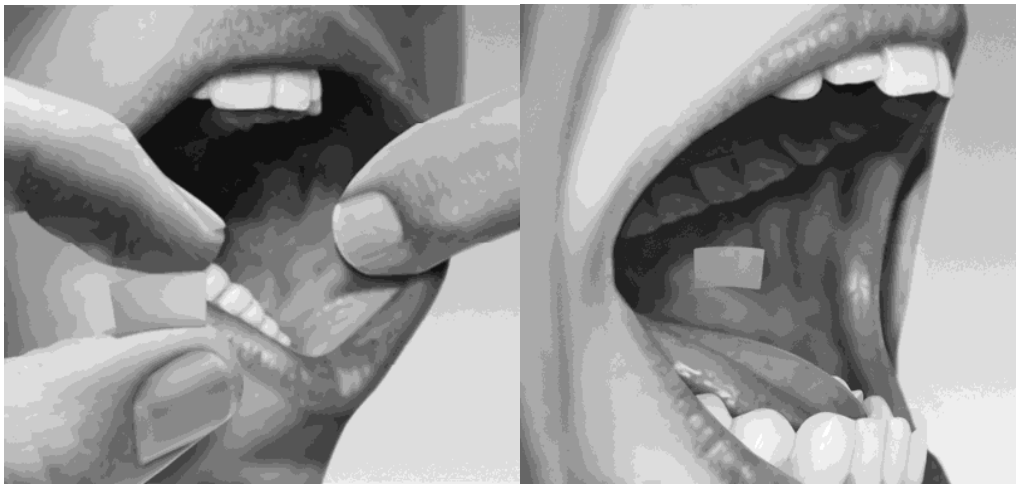

Figure 4

If your doctor tells you to take two films at a time, place the other film on the inside of the opposite cheek: and this will ensure that the films do not overlap. If your doctor tells you to take a third film, place it on the inside of your right or left cheek after the first two films have dissolved.

If you take more Suboxone than you should
Seek urgent medical attention if you or someone else takes too much of this medicine.
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
Stopping treatment suddenly may cause withdrawal symptoms. 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 have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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.
- 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).

Very common side effects (may affect more than one in 10 people):
Insomnia (inability to sleep), constipation, nausea, excessive sweating, headache, drug withdrawal syndrome.
Common side effects (may affect up to 1 in 10 people):
Weight loss, swelling of the hands and feet, drowsiness, anxiety, nervousness, tingling, depression, decreased sexual drive, increase in muscle tension, abnormal thinking, increased tearing (watering eyes) or other tearing disorders, flushing, increased blood pressure, migraines, runny nose, sore throat and painful swallowing, increased cough, upset stomach or other stomach discomfort, diarrhoea, mouth redness, 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, dizziness.
Uncommon side effects (may affect up to 1 in 100 people):
Swollen glands (lymph nodes), agitation, tremor, abnormal dreams, excessive muscle activity, depersonalisation (not feeling like yourself), medicine dependence, amnesia (memory disturbance), loss of interest, disturbance in attention, exaggerated feeling of wellbeing, convulsion (fits), speech disorder, small pupil size, difficulty urinating, blurred vision, eye inflammation or infection, rapid or slow heartbeat, low blood pressure, palpitations, heart attack, chest tightness, shortness of breath, asthma, yawning, mouth problems (sores, blisters, numbness, tingling, swelling, or pain), tongue discolouration or pain, 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, allergic reaction, loss of appetite, feelings of hostility, intoxication.
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 new-born babies, 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, causing dizziness, irritation or inflammation inside the mouth, including under the tongue.

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 or pharmacist. 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 this medicine 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 and the sachet. The expiry date refers to the last day of that month.
Store below 25 °C.
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 sachet safely.
Never open the sachet in advance.
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. Contents of the pack and other information

What Suboxone contains

- The active substances are buprenorphine and naloxone.
  Each 2 mg/0.5 mg film contains 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate).
  Each 4 mg/1 mg film contains 4 mg buprenorphine (as hydrochloride) and 1 mg naloxone (as hydrochloride dihydrate).
  Each 8 mg/2 mg film contains 8 mg buprenorphine (as hydrochloride) and 2 mg naloxone (as hydrochloride dihydrate).
  Each 12 mg/3 mg film contains 12 mg buprenorphine (as hydrochloride) and 3 mg naloxone (as hydrochloride dihydrate).

- The other ingredients are macrogol, maltitol liquid, natural lime flavour, hypromellose, citric acid, acesulfame potassium, sodium citrate, sunset yellow (E110) and white ink.

What Suboxone looks like and contents of the pack

Suboxone 2 mg/0.5 mg sublingual films are orange rectangular films of nominal dimensions 22.0 mm × 12.8 mm, with ‘N2’ imprinted in white ink.

Suboxone 4 mg/1 mg sublingual films are orange rectangular films of nominal dimensions 22.0 mm × 25.6 mm, with ‘N4’ imprinted in white ink.

Suboxone 8 mg/2 mg sublingual films are orange rectangular films of nominal dimensions 22.0 mm × 12.8 mm, with ‘N8’ imprinted in white ink.

Suboxone 12 mg/3 mg sublingual films are orange rectangular films of nominal dimensions 22.0 mm × 19.2 mm, with ‘N12’ imprinted in white ink.

The films are packed in individual sachets.
Pack sizes: cartons containing 7 × 1, 14 × 1 and 28 × 1 films.

Not all pack sizes may be marketed.

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This leaflet was last revised in {**month YYYY**}.

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