SUMMARY OF PRODUCT CHARACTERISTICS,
LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Subutex 0.4 mg sublingual tablets
Subutex 2 mg sublingual tablets
Subutex 8 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Subutex 0.4 mg sublingual tablets
Each tablet contains 0.4 mg buprenorphine (as buprenorphine hydrochloride).
Excipient(s) with known effect: lactose
For the full list of excipients, see section 6.1

Subutex 2 mg sublingual tablets
Each tablet contains 2 mg buprenorphine (as buprenorphine hydrochloride).
Excipient(s) with known effect: lactose
For the full list of excipients, see section 6.1

Subutex 8 mg sublingual tablets
Each tablet contains 8 mg buprenorphine (as buprenorphine hydrochloride).
Excipient(s) with known effect: lactose
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Sublingual tablet

Subutex 0.4 mg sublingual tablets
Uncoated oval white flat bevelled edged tablet, nominal dimensions 8 mm x 4 mm, debossed with “04” on one side.

Subutex 2 mg sublingual tablets
Uncoated oval white flat bevelled edged tablet, nominal dimensions 10 mm x 5 mm, debossed with “B2” on one side.

Subutex 8 mg sublingual tablets
Uncoated oval white flat bevelled edged tablet, nominal dimensions 14 mm x 7 mm, debossed with “B8” 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.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with buprenorphine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4). The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician

and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).

Posology
Treatment with Subutex sublingual tablets is intended for use in adults and children aged 16 years or over who have agreed to be treated for opioid dependence.

Precautions to be taken before dosing
Prior to treatment induction, physicians should be aware of the partial agonist profile of buprenorphine to the opiate receptors, which may precipitate a withdrawal syndrome in opioid-dependent patients and consideration should be given to the types 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 Subutex should be undertaken when objective and clear signs of withdrawal are evident e.g. a score higher than 12 on the Clinical Opioid Withdrawal Scale (COWS).

- **For patients dependent on heroin or short-acting opioids:** the first dose of buprenorphine should be started when objective signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.

- **For patients receiving methadone:** before beginning Subutex therapy, the dose of methadone should be reduced to a maximum of 30mg/day. Subutex may precipitate symptoms of withdrawal in patients dependent on methadone. The first dose of buprenorphine should be started only when objective signs of withdrawal appear and generally not less than 24 hours after the patient last used methadone because of the long half-life of methadone.

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy.

Induction:
The initial dose is from 0.8mg to 4mg, administered as a single daily dose.

Dosage adjustment and maintenance:
The dose of Subutex should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 32mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient.

Treatment goals, reducing dosage and discontinuation (Medical taper)
Before initiating treatment with buprenorphine, a treatment strategy including treatment duration and treatment goals, should be agreed together with the patient.
During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with buprenorphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4).
After a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose; when deemed appropriate, treatment may be discontinued in some patients. The availability of the sublingual tablet in doses of 0.4mg, 2mg and 8mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

Special populations

Elderly

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

Hepatic impairment
Patients who are positive for viral hepatitis, on concomitant medicinal products and / or have existing liver dysfunction are at risk of greater liver injury. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine (see section 4.4). Buprenorphine should be used with caution in patients with hepatic insufficiency (see section 5.2). Buprenorphine is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Renal impairment
Modification of the buprenorphine dose is not generally required for patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment, which may require dose adjustment (creatinine clearance < 30 ml/min) (see section 5.2).

Paediatric population
Subutex is contraindicated in children under the age of 16 (see section 4.3).

Method of administration
Administration is sublingual. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this drug. The tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
Children less than 16 years of age
Severe respiratory insufficiency
Severe hepatic insufficiency
Acute alcoholism or *delirium tremens*
Breast feeding

4.4 Special warnings and precautions for use

Subutex sublingual tablets are recommended only for the treatment of opioid drug dependence. It is also recommended that treatment is prescribed by a physician who ensures comprehensive management of the opioid-dependent patient(s).

Drug dependence, tolerance, potential for abuse and diversion
Prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else. Patients should be closely monitored for signs of misuse, abuse, or addiction. The clinical need for continuing opioid substitution therapy should be reviewed regularly.

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 infections, respiratory depression and hepatic injury. Buprenorphine misuse by someone other than the intended patient poses the additional risk of new drug dependent individuals using

buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft.

Sub-optimal treatment with buprenorphine may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine 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, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

Seizures
Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder.

Respiratory depression
A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines (see section 4.5) or when buprenorphine was not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol or other opioids. If buprenorphine is administered to some non-opioid dependent individuals who are not tolerant to the effects of opioids, potentially fatal respiratory depression may occur.

Subutex should be used with care in patients with respiratory insufficiency (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis).

Buprenorphine may cause severe, possibly fatal, respiratory depression in children and non-dependent persons who accidentally or deliberately ingest it. Protect children and non-dependent persons against exposure.

CNS depression
Buprenorphine may cause drowsiness particularly when used with alcohol or central nervous system depressants (such as benzodiazepines, tranquillisers, 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 and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe buprenorphine concomitantly with sedative medicines, 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 buprenorphine 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.

Tolerance and opioid use disorder (abuse and dependence)
Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type. Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce dependence, but at a lower level than a full agonist.
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as buprenorphine. Abuse or intentional misuse of buprenorphine may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).
Before initiating treatment with buprenorphine and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2).
Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psychoactive drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.
Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

Hepatitis and hepatic events
Cases of acute hepatic injury have been reported in opioid-dependent patients both in clinical trials and in post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing liver enzyme abnormalities, genetic disease, infection with hepatitis B or hepatitis C virus, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic drugs and ongoing injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing Subutex and during treatment. When a hepatic event is suspected further biological and etiological evaluation is required. Depending on the findings, Subutex may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If treatment is continued, hepatic function should be monitored closely.

All patients should have liver function tests performed at regular intervals.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with buprenorphine. The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).
Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.
If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Precipitation of opioid withdrawal syndrome
When initiating treatment with Subutex, it is important to be aware of the partial agonist profile of buprenorphine. Sublingually administered buprenorphine can precipitate withdrawal symptoms in opioid-dependent patients if administered before the agonist effects resulting from recent opioid use or misuse have subsided. To avoid precipitated withdrawal, induction should be undertaken when objective signs and symptoms of moderate withdrawal are evident (see section 4.2).

Hepatic impairment
The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study. Buprenorphine is extensively metabolized in the liver, plasma levels were found to be higher for buprenorphine in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of buprenorphine. Subutex sublingual tablets should be used with caution in patients with moderate hepatic impairment (see section 4.3 and 5.2). In patients with severe hepatic insufficiency the use of buprenorphine is contraindicated.

Renal impairment
Renal elimination plays a relatively small role (approximately 30%) in the overall clearance of buprenorphine; therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended dosing patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 5.2).

Use in adolescents
Due to lack of data in adolescents (age 16 – 18), patients in this age group should be more closely monitored during treatment.

General warnings related to the administration of opioids
Opioids may cause orthostatic hypotension in ambulatory patients.

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

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

Opioid-induced miosis, changes in the level of consciousness or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.

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

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

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

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'.

4.5 Interaction with other medicinal products and other forms of interaction

Subutex should not be taken together with:

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

Subutex should be used cautiously together with:

- sedatives such as benzodiazepines or related medicinal products: The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs 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 medicines should be limited (see section 4.4). Patients should be warned that it is extremely dangerous to self administer non-prescribed benzodiazepines whilst taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see section 4.4).

- **gabapentinoids:** the concomitant use of buprenorphine with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

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

- monoamine oxidase inhibitors (MAOI): Possible exacerbation of the effects of opioids, based on experience with morphine.

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

- opioid analgesics: Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. The potential for overdose also exists with a full agonist, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.

- naltrexone: This is an opioid antagonist that can block the pharmacological effects of buprenorphine. For opioid dependent patients currently receiving buprenorphine treatment, naltrexone may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms. For patients currently receiving naltrexone treatment, the intended therapeutic effects of buprenorphine administration may be blocked by naltrexone.

- CYP 3A4 inhibitors: An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving Subutex 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 and itraconazole, or 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 Subutex should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin or rifampicin) are co-administered. The dose of either buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

- concomitant administration of buprenorphine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of buprenorphine in pregnant women.
Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.
Towards the end of pregnancy, buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration 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.

Breast feeding

Buprenorphine and its metabolites are excreted in human breast milk. In rats, buprenorphine has been found to inhibit lactation. Therefore, breast feeding should be discontinued during treatment with Subutex (see section 4.3).

4.7 Effects on ability to drive and use machines

Buprenorphine has moderate influence on the ability to use machines when administered to opioid dependent patients. Subutex 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 section 4.4. and 4.5). Patients should be cautioned about operating hazardous machinery in case buprenorphine may affect their ability to engage in such activities.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Summary of safety profile

The most commonly reported adverse drug reactions were those related to withdrawal symptoms (e.g. insomnia, headache, nausea and hyperhidrosis) and pain.

Tabulated list of adverse reactions

Table 1 summarises:

- adverse reactions reported from pivotal clinical studies. The frequency of possible side effects listed below is defined using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), not known (cannot be estimated from the available data).
- the most commonly reported adverse drug reactions during post-marketing surveillance. Events occurring in at least 1% of reports by healthcare professionals and considered expected are included. Frequency of events not reported in pivotal studies cannot be estimated and is given as not known.

Table 1: Adverse effects observed in pivotal clinical studies and / or post marketing surveillance listed by body system

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Not known**
Infections and infestations		Bronchitis Infection Influenza Pharyngitis Rhinitis	
Blood and lymphatic system disorders		Lymphadenopathy	
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders	Insomnia	Agitation	Drug dependence (see section 4.4)

		Anxiety Depression Hostility Nervousness Paranoia Thinking abnormal	
Nervous system disorders	Headache	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor	Seizures
Eye disorders		Lacrimal disorder Mydriasis	
Cardiac disorders		Palpitations	
Vascular disorders		Vasodilatation	
Respiratory, thoracic and mediastinal disorders		Cough Dyspnoea Yawning	
Gastrointestinal disorders	Nausea	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Gastrointestinal disorder Flatulence Tooth disorder Vomiting	Dental caries
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash	
Musculoskeletal, connective tissue and bone disorders		Arthralgia Back pain Bone pain Muscle spasms Myalgia Neck pain	
Reproductive system and breast disorders		Dysmenorrhoea	
General disorders and administration site conditions	Drug withdrawal syndrome Pain	Asthenia Chest pain Chills Malaise Oedema peripheral Pyrexia	Drug withdrawal syndrome neonatal

Description of selected adverse reactions

The following is a summary of other post-marketing adverse event reports that are considered serious or otherwise noteworthy:

- In cases of intravenous misuse, 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 withdrawal effect similar to that associated with naloxone.
- The most common signs and symptoms of hypersensitivity include rashes, urticaria, and pruritus. Cases of bronchospasm, angioedema, and anaphylactic shock have been reported (see section 4.3).
- Transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy, and hepatic necrosis have occurred (see section 4.4).
- Drug dependence
  Repeated use of buprenorphine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).
- Neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder than that seen with a full μ-opioid agonist and may be delayed in onset. The nature of the syndrome may vary depending upon the mother's drug use history (see section 4.6).
- Hallucination, orthostatic hypotension, urinary retention and vertigo have been reported.

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 Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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. Preliminary symptoms of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and / or speech disorders.

Treatment
General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. 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. Use of an opioid antagonist (i.e., naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.

The long duration of action of buprenorphine should be taken into consideration when determining length of treatment needed to reverse the effects of an overdose. Naloxone can be cleared more rapidly than buprenorphine, allowing for a return of previously controlled buprenorphine overdose symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic group
Drugs used in opioid dependence ATC-code: N07BC01

Mechanism of action
Buprenorphine is an opioid partial agonist/antagonist which attaches itself to the μ (mu) k (kappa) receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible link with the μ receptors which, over a prolonged period, minimises the need of the opioid-dependent patient.

Clinical efficacy and safety
During clinical pharmacologic studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, "good effect" and respiratory depression.

5.2 Pharmacokinetic properties

Absorption
When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjungation in the small intestine. The use of this medication by oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose - concentration relationship is linear, between 2 mg and 16 mg.

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

Biotransformation and elimination
Buprenorphine is oxidatively metabolised by 14-N-dealkylation to N-desalkyl-buprenorphine (also known as norbuprenorphine) via cytochrome P450 CYP3A4 and by glucuroconjungation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is μ (mu) agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri- exponential, with long terminal elimination phase of 20-25 hours, due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule.

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a postmarketing study.

Table 2 summarizes the results from a clinical trial in which the exposure of buprenorphine was determined after administering a Suboxone 2.0/0.5mg (buprenorphine/naloxone) sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 2. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following buprenorphine/naloxone administration (change relative to healthy subjects)

PK Parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
Buprenorphine			
Cmax	1.2-fold increase	1.1-fold Increase	1.7-fold increase
AUC_{last}	Similar to control	1.6-fold increase	2.8-fold increase

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

5.3 Preclinical safety data

Acute toxicity of buprenorphine was determined in the mouse and rat following oral and parenteral administration. The median lethal doses (LD_{50}) in the mouse were 26, 94 and 261 mg/kg for intravenous, intraperitoneal and oral administration, respectively. The LD_{50} values in a rat were 35, 243 and 600 mg/kg for intravenous, intraperitoneal and oral administration, respectively.

When beagles were dosed continuously subcutaneously for one month, rhesus monkeys orally for one month and rats and baboons intramuscularly for six months, buprenorphine showed remarkably low tissue and biochemical toxicities.

From teratology studies in rats and rabbits, it was concluded that buprenorphine is not embryotoxic or teratogenic, and it does not have any marked effects on weaning potential. There were no adverse effects of fertility of general reproductive function in rats, although at the highest intramuscular dose (5mg/kg/day) the mothers experienced some difficulty in parturition and there was a high neonatal mortality.

Minimal to moderate hyperplasia of the bile duct with associated peribiliary fibrosis occurred in dogs following 52 weeks of oral dosing of 75mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monohydrated lactose
Mannitol
Maize starch
Povidone excipient K30
Citric acid

Sodium citrate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

7 or 28 tablets in nylon/aluminium/uPVC blister packs
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Indivior UK Limited
The Chapleo Building
Henry Boot Way
Priory Park, Hull
HU4 7DY
UK

8. MARKETING AUTHORISATION NUMBER(S)

Subutex 0.4 mg, sublingual tablets:	PL 36699/0001
Subutex 2 mg, sublingual tablets:	PL 36699/0002
Subutex 8 mg, sublingual tablets:	PL 36699/0003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

February 1998 (UK)

10. DATE OF REVISION OF THE TEXT

October 2025

11. LEGAL CATEGORY

CD (Sch 3), POM

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 7 and 28 TABLETS 0.4MG STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Subutex 0.4 mg sublingual tablets
BUPRENORPHINE HYDROCHLORIDE

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains buprenorphine hydrochloride equivalent to 0.4 mg buprenorphine base.

3. LIST OF EXCIPIENTS

Also contains monohydrated lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

7 sublingual tablets
28 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Directions for use: Sublingual use. Place under the tongue and allow to dissolve. Do not swallow or chew the tablet. Use as directed by a physician. Do not exceed the prescribed dose.

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

Precautions/Warnings/Contraindications: see insert

This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for more information.

Can cause addiction
Contains opioid

8. EXPIRY DATE

EXP:
Mfg Date:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

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

None

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Indivior UK Limited
The Chapleo Building
Henry Boot Way
Priory Park, Hull
HU4 7DY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

United Kingdom: PL 36699/0001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Subutex 0.4mg 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 0.4MG STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Subutex 0.4mg sublingual tablets
Buprenorphine Hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Peel here

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 7 and 28 TABLETS 2MG STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Subutex 2 mg sublingual tablets
BUPRENORPHINE HYDROCHLORIDE

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains buprenorphine hydrochloride equivalent to 2 mg buprenorphine base.

3. LIST OF EXCIPIENTS

Also contains monohydrated lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

7 sublingual tablets
28 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Directions for use: Sublingual use. Place under the tongue and allow to dissolve. Do not swallow or chew the tablet. Use as directed by a physician. Do not exceed the prescribed dose.

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

Precautions/Warnings/Contraindications: see insert

This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for more information.

Can cause addiction
Contains opioid

8. EXPIRY DATE

EXP:
Mfg Date:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

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

None

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Indivior UK Limited
The Chapleo Building
Henry Boot Way
Priory Park, Hull
HU4 7DY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

United Kingdom: PL 36699/0002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Subutex 2mg 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 2MG STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Subutex 2mg sublingual tablets
Buprenorphine Hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Peel here

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PACK OF 7 and 28 TABLETS 8MG STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Subutex 8 mg sublingual tablets
BUPRENORPHINE HYDROCHLORIDE

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains buprenorphine hydrochloride equivalent to 8 mg buprenorphine base.

3. LIST OF EXCIPIENTS

Also contains monohydrated lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

7 sublingual tablets
28 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Directions for use: Sublingual use. Place under the tongue and allow to dissolve. Do not swallow or chew the tablet. Use as directed by a physician. Do not exceed the prescribed dose.

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

Precautions/Warnings/Contraindications: see insert

This medicine can make you feel sleepy. Do not drive while taking this medicine until you know how it makes you feel. See the leaflet inside for more information.

Can cause addiction
Contains opioid

8. EXPIRY DATE

EXP:
Mfg Date:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

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

None

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Indivior UK Limited
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HU4 7DY
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

United Kingdom: PL 36699/0003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Subutex 8mg 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 8MG STRENGTH

1. NAME OF THE MEDICINAL PRODUCT

Subutex 8mg sublingual tablets
Buprenorphine Hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Indivior UK Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

Peel here

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Subutex 0.4 mg, 2 mg and 8 mg sublingual tablets
buprenorphine

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:

This medicine contains buprenorphine which is an opioid, which can cause addiction. You can get withdrawal symptoms if you stop taking it suddenly.

1. WHAT SUBUTEX IS AND WHAT IT IS USED FOR

Subutex is used to treat dependence on opiate (narcotic) drugs, such as morphine and heroin in drug addicts who have agreed to be treated for their addiction.
Subutex is used in adults and adolescents over 16 years of age who are also receiving medical, social and psychological support.

This medicine contains buprenorphine which belongs to a class of medicines called opioids.
This medicine has been prescribed to you and should not be given to anyone else. Opioids can cause addiction and you may get withdrawal symptoms if you stop taking it suddenly. Your prescriber should have explained how long you will be taking it for and when it is appropriate to stop, how to do this safely.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE SUBUTEX

Do not take Subutex:
- If you are a child under the age of 16 years.
- If you are allergic to buprenorphine 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 breast feeding a baby.

Warnings and precautions
Talk to your doctor before taking Subutex if you have:

- seizures, fits or convulsions
- asthma or other breathing problems
- any liver disease such as hepatitis
- low blood pressure
- recently suffered head injury or brain disease
- a urinary disorder (especially linked to enlarged prostate 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 Subutex can lead to serotonin syndrome, a potentially life-threatening condition (see ''Other medicines and Subutex'').

Important things to be aware of:

- **<u>Misuse, abuse and diversion</u>**
  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. Opioids should only be used by those they are prescribed for. **Do not give your medicine to anyone else**. Taking higher doses or more frequent doses of opioid may increase the risk of addiction. Overuse and misuse can lead to overdose and/or death.

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

- **Tolerance, dependence and addiction**
  This medicine contains buprenorphine which is an opioid medicine. Repeated use of opioids can result in the drug being less effective (you become accustomed to it, known as tolerance). Repeated use of buprenorphine can also lead to dependence, abuse, and addiction, which may result in life-threatening overdose.
  Dependence or addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it.
  The risk of becoming dependent or addicted varies from person to person. You may have a greater risk of becoming dependent on or addicted to buprenorphine if:
  - You or anyone in your family have ever abused or been dependent on alcohol, prescription medicines or illegal drugs ("addiction").
  - You are a smoker.
  - You have ever had problems with your mood (depression, anxiety, or a personality disorder) or have been treated by a psychiatrist for other mental illnesses.
  If you notice any of the following signs whilst taking buprenorphine, it could be a sign that you have become dependent or addicted:
  – You need to take the medicine for longer than advised by your doctor
  – You need to take more than the recommended dose
  – You are using the medicine for reasons other than prescribed, for instance, 'to stay calm' or 'help you sleep'
  – You have made repeated, unsuccessful attempts to quit or control the use of the medicine

– When you stop taking the medicine you feel unwell, and you feel better once taking the medicine again ('withdrawal effects')
If you notice any of these signs, speak to your doctor to discuss the best treatment pathway for you, including when it is appropriate to stop and how to stop safely (See section 3, If you stop using Subutex).

- **Addiction and withdrawal symptoms**
  Taking this medicine regularly, particularly for a long time, can lead to addiction.

  Addiction can cause withdrawal symptoms when you stop taking this medicine. Withdrawal symptoms can include restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, loss of appetite, shaking, shivering or sweating. Your prescriber will discuss with you how to gradually reduce your dose before stopping the medicine. It is important that you do not stop taking the medicine suddenly as you will be more likely to experience withdrawal symptoms.

  This product can cause withdrawal symptoms if you take it less than 6 hours after you use a short-acting opioid (e.g. morphine, heroin) or less than 24 hours after you use a long-acting opioid such as methadone.

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

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

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

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

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

- Benzodiazepines (used to treat anxiety or sleep disorders) such as diazepam, temazepam, alprazolam. Concomitant use of Subutex 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 Subutex 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.

- Gabapentin or pregabalin to treat epilepsy or pain due to nerve problems (neuropathic pain).
- Anti-depressants, such as moclobemide, tranylcypromine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine. These medicines may interact with Subutex 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.
- **Other medicines that may make you feel sleepy** which are used to treat illnesses such as anxiety, sleeplessness, convulsions / seizures, pain. These types of medicines will reduce your alertness levels making it difficult for you to drive and use machines. They may also cause central nervous system depression, which is very serious. Below is a list of examples of these types of medicines:
  - other opioid containing medicines such as methadone, certain pain killers and cough suppressants.
  - antidepressants (used to treat depression) such as isocarboxazide, phenelzine, selegeline, 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.
- Naltrexone may prevent Subutex from working. If you take naltrexone whilst you are taking Subutex you may experience a sudden onset of prolonged and intense withdrawal symptoms.
- Clonidine (used to treat high blood pressure) may extend the effects of this medicine.
- Anti-retrovirals (used to treat AIDS) such as ritonavir, nelfinavir, indinavir may increase the effects of this medicine.
- Some antifungal agents (used to treat fungal infections) such as ketoconazole and itraconazole and certain antibiotics (macrolide) may extend the effects of this medicine.
- Medicines used to treat allergies, travel sickness or nausea (antihistamines or antiemetics);
- Medicines to treat psychiatric disorders (antipsychotics or neuroleptics);
- Muscle relaxants;
- Medicines to treat Parkinson's disease.
- Some medicines may decrease the effect of Subutex. These include medicines used to treat epilepsy (such as carbamazepine and phenytoin) and medicines used to treat tuberculosis (rifampicin).

To get the greatest benefit from taking Subutex, you must tell your doctor about all the medicines you are taking, including alcohol, medicines containing alcohol, street drugs, and any prescription medicine you are taking that has not been prescribed for you by your doctor.

Subutex with food, drink and alcohol

Alcohol may increase drowsiness and may increase the risk of respiratory failure (inability to breathe) if taken with Subutex. **Do not take Subutex together with alcohol.** Do not swallow or consume food or 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 or pharmacist for advice before taking this medicine.

Do not take Subutex if you are pregnant or think you might be pregnant unless you have discussed this with your prescriber and the benefits of treatment are considered to outweigh the potential harm to the baby.

If you use Subutex during pregnancy, your baby may become dependent and experience withdrawal symptoms including problems with breathing after the birth which may need to be treated. These symptoms may occur several days after birth.

Do not take Subutex while you are breastfeeding as buprenorphine passes into breast milk and will affect your baby.

Driving and using machines

If you feel drowsy or dizzy while taking these tablets do not use machinery.

The medicine can affect your ability to drive as it may make you sleepy or dizzy.

- Do not drive while taking this medicine until you know how it affects you.
- It is an offence to drive if this medicine affects your ability to drive.
- However, you would not be committing an offence if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber or in the information provided with the medicine and
    - It was not affecting your ability to drive safely

Talk to your doctor or pharmacist if you are not sure whether it is safe for you to drive while taking this medicine.

Subutex 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) per tablet, that is to say essentially 'sodium-free'.

3. HOW TO TAKE SUBUTEX

You must place the tablet under your tongue (sublingual) and allow it to dissolve, which will take 5 to 10 minutes. This is the only way to take the tablets. Do not chew or swallow them whole, as they will not work.

Your doctor will tell you how many tablets to take and you should always follow this advice.

To avoid sudden withdrawal symptoms, treatment with Subutex should be given when there are already clear signs of withdrawal symptoms.

Your prescriber should discuss your treatment and whether you need to continue taking tablets at regular intervals. If you and your prescriber decide to stop treatment, a plan will be put in place to gradually reduce the dose and stop taking the medicine to minimise the risk of withdrawal effects.

Adults and children over the age of 16 years: when beginning treatment the dose is between 0.8 to 4mg, taken once a day.

For drug addicts who have not had any withdrawal treatment: one dose of Subutex should be taken at least 6 hours after the last use of the opioid (narcotic such as morphine or heroin), or when the first signs of craving appear. If you take it less than six hours after you use a narcotic you may get withdrawal symptoms.

For patients taking methadone: before beginning treatment, your doctor should reduce your dose of methadone to not more than 30mg a day. Subutex may cause withdrawal symptoms in patients who are dependent on methadone if used within 24 hours of the last dose of methadone.

During your treatment, your doctor may increase your dose of Subutex, to a maximum single daily dose of 32mg, depending upon your response. Once you have been stable for a while, your doctor will gradually reduce your dose and it may be possible to stop it altogether. Do not suddenly stop taking the tablets, as this may cause withdrawal symptoms.

If you take more Subutex 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 as overdose with Subutex may cause serious and life-threatening breathing problems.

If you forget to take Subutex

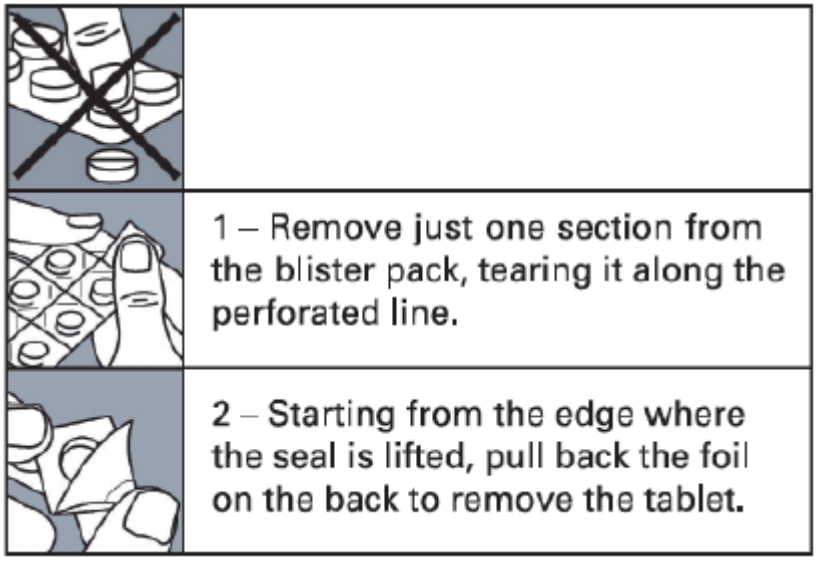
Tell your doctor as soon as possible if you miss a dose and follow his or her instructions. Do not take a double dose to make up for the forgotten dose.

If you stop taking Subutex

Do not change the treatment in any way or stop treatment without the agreement of the doctor who is treating you. Do not suddenly stop taking this medicine. If you want to stop taking this medicine, discuss this with your prescriber first. They will tell you how to do this, usually by reducing the dose gradually so that any unpleasant withdrawal effects are kept to a minimum. Withdrawal symptoms such as restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, shaking, shivering or sweating may occur if you suddenly stop taking this medicine.

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

How to remove the tablet from the blister pack



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:

- sudden wheezing, difficulty breathing, swelling of the eyelids, face, tongue, lips, throat or hands; rash or itching especially those covering your whole body. These may be signs of a life-threatening allergic reaction.
- if you start to breathe more slowly or weakly than expected (respiratory depression).
- if you start to feel faint, as this may be a sign of low blood pressure.

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

- severe fatigue (tiredness), have no appetite or if your skin or eyes look yellow. These may be symptoms of liver damage.

The frequency of possible side effects listed below is defined using the following convention:

- very common (affects more than 1 user in 10)
- common (affects 1 to 10 users in 100)
- not known (frequency cannot be estimated from the available data).

Side effects reported with Subutex
Very common side effects:
Drug withdrawal syndrome, headache, hyperhidrosis (sweating), insomnia (inability to sleep), nausea (feeling sick), pain
Common side effects:
Abdominal pain, agitation, anxiety, joint pain, weakness, back pain, bone pain, bronchitis, chest pain, chills, constipation, cough, decreased appetite, depression, diarrhoea, dizziness, dry mouth, painful period, indigestion, shortness of breath, flatulence, gastrointestinal disorder, hostility, increase in muscle tension, infection, influenza, nervousness, tearing (watery eyes) disorder, swollen glands (lymph nodes), malaise,

migraine, muscle spasms, muscle pain, dilation of the pupil, neck pain, palpitations, paranoia, burning or tingling in hands and feet, swelling (hands and feet), runny or stuffy nose, sore throat and painful swallowing, fever, rash, somnolence, syncope (fainting), thinking abnormal, tooth disorder, tremor; flushing, vomiting (being sick), yawning
Frequency not known:
Dental caries, drug dependence and addiction, seizures, drug withdrawal syndrome in newborn, hallucinations (sensing things that are not real), drop in blood pressure on changing position from sitting or lying down to standing, difficulty in urinating, vertigo Misusing this medicine by injecting it can cause withdrawal symptoms, infections, other skin reactions and potentially serious liver problems

Drug Withdrawal
When you stop taking Subutex, you may experience drug withdrawal symptoms, which include restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, shaking, shivering or sweating.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE SUBUTEX

Keep out of the sight and reach of children. Store this medicine in a safe and secure place, where other people cannot access it. It can cause serious harm and be fatal to people who may take this medicine by accident, or intentionally when it has not been prescribed for them.

Do not store above 30°C.
Store in the original package in order to protect from moisture.
Do not use this medicine after the expiry date which is stated on the carton after EXP.

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 Subutex contains

The active substance is buprenorphine (as buprenorphine hydrochloride).
Each sublingual tablet contains 0.4mg, 2mg or 8mg of buprenorphine.
The other ingredients are monohydrated lactose, mannitol, maize starch, povidone K30, citric acid, magnesium stearate and sodium citrate.

What Subutex looks like and contents of the pack

Subutex 0.4mg sublingual tablets are uncoated oval white tablets of 8 mm x 4 mm, debossed with “04” on one side.

Subutex 2mg sublingual tablets are uncoated oval white tablets of 10 mm x 5 mm, debossed with “B2” on one side.

Subutex 8mg sublingual tablets are uncoated oval white tablets of 14 mm x 7 mm, debossed with “B8” on one side.

The sublingual tablets come in blister packs containing either 7 or 28 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Indivior UK Limited
The Chapleo Building
Henry Boot Way
Priory Park, Hull
HU4 7DY
UK

Manufacturer:
Reckitt Benckiser Healthcare (UK) Limited
Dansom Lane
Hull, HU8 7DS
UK

For any information about this medicine, please contact the Marketing Authorisation Holder:
Indivior UK Limited
Telephone 0808 234 9243
PatientSafetyRoW@indivior.com

This leaflet was last revised in October 2025.