1. NAME OF THE MEDICINAL PRODUCT

SUBUTEX SUBLINGUAL TABLETS 0.4 mg
SUBUTEX SUBLINGUAL TABLETS 2 mg
SUBUTEX SUBLINGUAL TABLETS 8 mg

Brand of buprenorphine

FOR SUBLINGUAL ADMINISTRATION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Buprenorphine hydrochloride equivalent to buprenorphine base: 0.4mg, 2 mg or 8 mg.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Each SUBUTEX contains buprenorphine hydrochloride equivalent to 0.4mg, 2mg or 8mg buprenorphine base.
SUBUTEX 8mg sublingual tablets are uncoated oval white flat bevelled edged tablets, nominal dimensions 14 mm x 7 mm, debossed on one side with "B8".
SUBUTEX 2 mg sublingual tablets are uncoated oval white flat bevelled edged tablets, nominal dimensions 10 mm x 5 mm, debossed on one side with "B2".
SUBUTEX 0.4 mg sublingual tablets are uncoated oval white flat bevelled edged tablets, nominal dimensions 8 mm x 4 mm, debossed on one side with "04".

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment.

4.2 Posology and method of administration:

Treatment with SUBUTEX is intended for use in adults and children over 15 years of age who have agreed to be treated for addiction.

When initiating SUBUTEX treatment, the physician should be aware of the partial agonist profile of the buprenorphine molecule. Buprenorphine binds to the μ (mu) and κ (kappa) opiate receptors, and may precipitate withdrawal symptoms in opioid-dependent patients.

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 five to ten minutes.

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

- *for opioid-dependent drug addicts who have not undergone withdrawal:* one dose of SUBUTEX tablet(s) administered sublingually at least 4 hours after the last use of the opioid, or when the first signs of craving appear.
- *for patients receiving methadone:* before beginning SUBUTEX therapy, the dose of methadone should be reduced to a maximum of 30 mg/day. **SUBUTEX may precipitate symptoms of withdrawal in patients dependent upon methadone.**

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 32 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient.

Dosage reduction and termination of treatment: After a satisfactory period of stabilization 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 0.4 mg, 2 mg and 8 mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

4.3 Contraindications:
Hypersensitivity to buprenorphine or any other component of the tablet; severe respiratory insufficiency; severe hepatic insufficiency; acute alcoholism or delirium tremens.

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).

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 localized 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 minimize the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's level of stability.

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.

Hepatitis, 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.

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).

This product can cause opioid withdrawal symptoms if administered to an addicted patient less than 4 hours after the last use of the drug. (See section 4.2)

As buprenorphine is an opioid, pain as a symptom of a disease may be attenuated. This may interfere with early detection of the disease state.

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.

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

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

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 hepatic impairment (see section 4.3 and 5.2). Patients who are positive for viral hepatitis, on concomitant medicinal products and / or have existing liver dysfunction are at risk of greater liver injury.

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).

CNS depression: SUBUTEX may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants. (such as benzodiazepines, tranquillisers, sedatives or hypnotics) (see sections 4.5 and 4.7).

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

No data are available in children under 15 years of age; therefore, SUBUTEX should not be used in children under the age of 15.

Allergic reactions: Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, urticaria, and pruritus. Cases of bronchospasm, angioedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to SUBUTEX use.

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

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.
Alcohol increases the sedative effect of buprenorphine, which can make driving vehicles and operating machinery hazardous.

SUBUTEX should be used cautiously together with:
Benzodiazepines: This combination may potentiate respiratory depression of central origin, with risk of death; therefore, dosages must be limited. The risk of drug abuse should also be considered. (See section 4.4). There have been a number of reports in the post-marketing experience of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by drug abusers. In many of these cases, buprenorphine was misused by self-injection of crushed SUBUTEX tablets. SUBUTEX should be prescribed with caution to patients on benzodiazepines or other drugs that act on the central nervous system, regardless of whether these drugs are taken on the advice of a physician or are taken as drugs of abuse.

Other central nervous system depressants; other opioid derivatives (analgesics and antitussives); certain antidepressants, sedative H_1 -receptor antagonists, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. This combination increases central nervous system depression and can make driving vehicles and operating 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.

Monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.

CYP 3A4 inhibitors: An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax 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.

A suspected interaction between buprenorphine injection and phenprocoumon, resulting in purpura, has been reported.

Naltrexone and other opioid agonists: Since buprenorphine is a partial mu-opioid agonist, concomitantly administered opioid antagonists such as naltrexone can reduce or completely block the effects of buprenorphine. Patients maintained on SUBUTEX may experience a sudden onset of prolonged and intense opioid withdrawal symptoms if dosed with opioid antagonists that achieve pharmacologically relevant systemic concentrations.

4.6 Pregnancy and lactation:

Pregnancy

There are no adequate data from the use of buprenorphine in pregnant women.
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.

Consequently, the use of buprenorphine is not recommended during pregnancy.

Breast feeding

Buprenorphine and its metabolites are excreted in human breast milk. In rats, buprenorphine has been found to inhibit lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBUTEX sublingual tablets and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

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.

4.8 Undesirable effects:

Summary of the 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 summarizes:

• 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).

• 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)**	**Frequency 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 Anxiety Depression Hostility Nervousness Paranoia Thinking abnormal	Drug dependence
Nervous system disorders	Headache	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope	

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)**	**Frequency not known**
		Tremor	
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	
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	Drug withdrawal syndrome neonatal

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)**	**Frequency not known**
		Malaise Oedema peripheral Pyrexia	

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).
- 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.

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

Treatment

In the event of accidental overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the

patient vomits, care must be taken to prevent aspiration of the vomitus.
Symptomatic treatment of respiratory depression, following standard intensive care measures, should be performed. 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. If an opioid antagonist (i.e., naloxone) is used, the long duration of action of SUBUTEX 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:

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

Buprenorphine has a wide margin of safety due to its partial agonist/antagonist activity, which limits its depressant effects, particularly on cardiac and respiratory functions.

5.2 Pharmacokinetic properties:

Absorption:

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N- dealkylation and glucuroconjugation in the small intestine and the liver. The use of this medication by the 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 metabolized by 14-N dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. The N-dealkybuprenorphine is a μ (mu) agonist with weak intrinsic activity. Preclinical data suggest that CYP3A4 is responsible for the N-dealkylation of buprenorphine.

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase of 20 to 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 feces by biliary excretion of the glucuroconjugated metabolites (80%), 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 3 summarizes the results from a clinical trial in which the exposure of buprenorphine and naloxone 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 the 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. In one oral study of one year in dogs, a hepatic toxicity has been observed at very high dose (75mg/kg).

Teratology and reproduction studies in intramuscularly dosed rats and rabbits showed that buprenorphine was not embryotoxic, embryolethal or teratogenic and did not have an adverse effect on weaning. There were no adverse effects on fertility or general reproduction function in rats.

Carcinogenicity series in mice and rats show that there is no difference in the incidence of different tumour types between control and buprenorphine treated animals. However, in a study conducted with pharmacological doses in mice, atrophy and a tubular mineralization of testis have been evidenced in treated animals.

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

None known.

6.3 Shelf life:

Shelf-life information can be found on the outer carton of the product.

6.4 Special precautions for storage:

Store below 30^{o} C in a dry place. Keep out of reach of children.

6.5 Nature and contents of container:

Sublingual tablets in blister packs of 7 and 28 tablets.

Further information can be obtained from the doctor or pharmacist.

Manufactured by Reckitt Benckiser Healthcare (UK) Ltd, Dansom Lane, Hull, HU8 7DS, UK.
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