SCHEDULING STATUS **S6**

1. NAME OF THE MEDICINE

SUBUTEX SUBLINGUAL 0,4 mg tablets

SUBUTEX SUBLINGUAL 2 mg tablets

SUBUTEX SUBLINGUAL 8 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SUBUTEX SUBLINGUAL 0,4 mg:

Each tablet contains buprenorphine hydrochloride equivalent to 0,4 mg buprenorphine base.

Excipients with known effect:

Sugar content: Each tablet contains 29,626 mg lactose monohydrate and 18,0 mg mannitol.

SUBUTEX SUBLINGUAL 2 mg:

Each tablet contains buprenorphine hydrochloride equivalent to 2,0 mg buprenorphine base.

Excipients with known effect:

Sugar content: Each tablet contains 47,94 mg lactose monohydrate and 30,0 mg mannitol.

SUBUTEX SUBLINGUAL 8 mg:

Each tablet contains buprenorphine hydrochloride equivalent to 8,0 mg buprenorphine base.

Excipients with known effect:

Sugar content: Each tablet contains 191,76 mg lactose monohydrate and 120,0 mg mannitol.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SUBUTEX SUBLINGUAL 0,4 mg:

Oval, flat, glossy, white to creamy-white tablet with “04” on the one side.

SUBUTEX SUBLINGUAL 2 mg:

Oval, flat, glossy, white to creamy-white tablet with “B2” on the one side.

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SUBUTEX SUBLINGUAL 8 mg:

Oval, flat, glossy, white to creamy-white tablet with “B8” on the 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 SUBUTEX SUBLINGUAL 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 is intended for use in adults and children over 15 years of age who have agreed to be treated for opioid dependence.

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

Induction Therapy:

The initial dose is from 0,8 mg to 4 mg, administered as a single daily dose.

- ***For opioid-dependent patients who have not undergone withdrawal:*** one dose of SUBUTEX SUBLINGUAL administered sublingually at least 4 hours after the last use of the opioid, or when the first signs of craving appear.

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- ***For patients receiving methadone:*** Before beginning SUBUTEX SUBLINGUAL therapy, the dose of methadone should be reduced to a maximum of 30 mg/day. SUBUTEX SUBLINGUAL may precipitate symptoms of withdrawal in patients dependent upon methadone.

Dosage adjustment and maintenance:

The dose of SUBUTEX SUBLINGUAL should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 16 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 stabilisation has been achieved, the dosage should be reduced gradually to a lower dose; when deemed appropriate, treatment should be discontinued. The availability of the sublingual tablet in doses of 0,4 mg, 2,0 mg and 8,0 mg, 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 have not been established.

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, and plasma levels were found to be higher for buprenorphine in patients with moderate and severe hepatic impairment compared to healthy subjects. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX SUBLINGUAL should be used with caution in patients with moderate to severe hepatic impairment (see section 5).

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

Patients who are positive for viral hepatitis, on concomitant medicinal products (see section 4.5) and/or have existing liver dysfunction are at greater risk of liver injury. Regular monitoring of liver function is recommended (see section 4.4).

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 (CLcr < 30 ml/min), which may require dose adjustment.

Paediatric population

No data are available in children less than 15 years of age; therefore, SUBUTEX SUBLINGUAL should not be used in children under the age of 15 (see section 4.3).

Method of administration

Administration is sublingual.

Physicians must advise patients that the tablet should not be swallowed.

4.3 Contraindications

Hypersensitivity to buprenorphine or to any of the excipients listed in section 6.1; severe respiratory insufficiency; severe hepatic insufficiency; alcoholism or delirium tremens.

This product should not be used in patients with asthma or respiratory insufficiency as respiratory depression may occur with SUBUTEX SUBLINGUAL.

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

4.4 Special warnings and precautions for use

SUBUTEX SUBLINGUAL is recommended only for the treatment of opioid drug dependence.

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Drug dependence, tolerance, potential for abuse and diversion:

Prolonged use of this medicine 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.

SUBUTEX SUBLINGUAL can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral infections, respiratory depression and hepatic injury.
SUBUTEX SUBLINGUAL 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 SUBUTEX SUBLINGUAL may prompt medication misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with SUBUTEX SUBLINGUAL may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

To minimise the risk of misuse, abuse and diversion, appropriate precautions should be taken when prescribing and dispensing SUBUTEX SUBLINGUAL, 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.

Sleep-related breathing disorders:

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

Respiratory depression:

A number of cases of death due to respiratory depression have been reported, particularly when SUBUTEX SUBLINGUAL was used in combination with benzodiazepines (see section 4.5), when high dose buprenorphine was administered to non-opioid dependent individuals who had not developed a tolerance to the effects of opioids, or when buprenorphine was otherwise not used according to prescribing information. Deaths have also been reported in association with concomitant administration of buprenorphine and other CNS depressants (see section 4.5).

SUBUTEX SUBLINGUAL may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

SUBUTEX SUBLINGUAL should be used with caution in patients with compromised respiratory function (e.g. chronic obstructive pulmonary disease, asthma, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis).

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

CNS depression:

SUBUTEX SUBLINGUAL may cause drowsiness, particularly when used together with alcohol or central nervous system depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics) (see sections 4.5 and 4.7).

Risk from concomitant use of sedative medicines such as benzodiazepines or related medicines:

Concomitant use of SUBUTEX SUBLINGUAL and sedative medicines such as benzodiazepines or related medicines 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 SUBUTEX SUBLINGUAL concomitantly with sedative medicines, the lowest effective dose 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 SUBUTEX SUBLINGUAL and other serotonergic medicines, 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 medicines is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Dependence:

Buprenorphine is a partial agonist at the μ (mu)-opiate receptor and chronic administration produces dependence of the opioid type, but at a lower level than a full agonist (e.g., morphine). The withdrawal syndrome is typically milder than seen with full agonists, and may be delayed in onset.

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

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Hepatitis and hepatic events:

Cases of acute hepatic injury have been reported in opioid-dependent patients, both in clinical trials and in post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, viral infection such as hepatitis B and chronic hepatitis C, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic medicines, or ongoing drug use by injection) may have a causative or contributory role.

Patients who are positive for viral hepatitis, on concomitant medicinal products (see section 4.5) and/or have existing liver dysfunction are at greater risk of liver injury, and these underlying factors must be taken into consideration before prescribing SUBUTEX SUBLINGUAL and during treatment (see section 4.2).

When a hepatic event is suspected, further biological and etiological evaluation is required.

Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.

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 SUBUTEX SUBLINGUAL. 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.

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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 medicine 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 SUBLINGUAL, it is important to be aware of buprenorphine's partial agonist profile. 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 precipitating withdrawal upon induction from short-acting or long-acting opioids, the patient should show objective signs and symptoms of moderate withdrawal prior to induction dosing.

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

Hepatic impairment:

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study. Since buprenorphine is extensively metabolized, plasma levels were found to be elevated for buprenorphine in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. SUBUTEX SUBLINGUAL should be used with caution in patients with moderate to severe hepatic impairment (see section 5.2).

Renal impairment:

Renal elimination plays a relatively small role in the overall clearance of buprenorphine; therefore, no dose modification based on renal function is generally required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CLcr <30 ml/min) (see section 4.2).

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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 SUBLINGUAL use.

General opioid class warnings:

- Opioids may produce orthostatic hypotension in ambulatory patients.
- Opioids may elevate cerebrospinal fluid pressure, which may cause seizures, so opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.
- 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 should be used with caution in patients with toxic psychoses, acute alcoholism, or delirium tremens.
- Opioids should be used with caution in patients with hypotension, prostatic hypertrophy or urethral stricture.
- 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.

Paediatric population

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

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

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Excipients

SUBUTEX SUBLINGUAL contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g., galactosaemia, glucose-galactose malabsorption should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

SUBUTEX SUBLINGUAL should be used cautiously together with:

Alcohol: Alcohol increases the sedative effect of SUBUTEX SUBLINGUAL. SUBUTEX SUBLINGUAL should not be used together with alcoholic drinks, and must be used cautiously with medicines containing alcohol (see section 4.4).

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

Other central nervous system depressants: Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects. The reduced level of alertness can make driving and using machines hazardous.

Example central nervous system depressants are: other opioids (e.g., methadone, analgesics, antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine and related substances.

Opioid analgesics: The analgesic properties of other opioids such as methadone and level III analgesics may be reduced in patients receiving treatment with buprenorphine for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine.

Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or level III analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.

Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists (see section 4.4).

Naltrexone: Naltrexone is an opioid antagonist that can block the pharmacological effects of buprenorphine.

For opioid dependent patients currently receiving SUBUTEX SUBLINGUAL treatment, the naltrexone antagonist may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms.

For patients currently receiving naltrexone treatment, the intended therapeutic effects of SUBUTEX SUBLINGUAL administration may be blocked by the naltrexone antagonist.

CYP3A4 inhibitors: Patients receiving SUBUTEX SUBLINGUAL should be closely monitored, and may require dose reduction if combined with potent CYP3A4 inhibitors.

An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC (area under the curve) of buprenorphine (approximately 50 % and 70 % respectively) and, to a lesser extent, of norbuprenorphine. Example CYP3A4 inhibitors include

protease inhibitors (e.g., ritonavir, indinavir and saquinavir), macrolide antibiotics (e.g., TAO), gestodene and azole antifungals (e.g., ketoconazole).

CYP3A4 inducers: Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in under-treatment of opioid dependence with buprenorphine. It is recommended that patients receiving SUBUTEX SUBLINGUAL should be closely monitored if inducers (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered, and the dose of buprenorphine or CYP3A4 inducer may need to be adjusted accordingly.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety in pregnant women has not been established. Chronic use of SUBUTEX SUBLINGUAL by the mother at the end of pregnancy may result in a withdrawal syndrome (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions) in the neonate.
The syndrome is generally delayed for several hours to several days after birth.
Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Breastfeeding

Buprenorphine has the potential to inhibit lactation or milk production. In addition, because buprenorphine passes into the mother's milk, breast-feeding is contra-indicated

Fertility

No data on male and female fertility is available.

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4.7 Effects on ability to drive and use machines

SUBUTEX SUBLINGUAL has moderate influence on the ability to drive and use machines when administered to opioid dependent patients. This product may cause drowsiness, dizziness, or impaired thinking, especially during treatment induction and dose adjustment. If used with alcohol or central nervous system depressants the effect is likely to be more pronounced (see section 4.5). Patients should be cautioned about operating hazardous machinery, including driving motor vehicles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities.

4.8 Undesirable effects

The onset of side-effects depends on the patient's tolerance threshold, which is higher in opioid-dependent patients than in the general population.

a. 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.
In patients with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

b. Tabulated summary 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), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000).

Table 1. Treatment-related undesirable effects reported by body system in clinical studies of SUBUTEX SUBLINGUAL		
System organ class	***Frequency***	***Adverse Event***

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Infections and infestations	Common	Bronchitis Infection Influenza Pharyngitis Rhinitis
Blood and lymphatic system disorders	Common	Lymphadenopathy
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Very common	Insomnia
	Common	Agitation Anxiety Depression Hostility Nervousness Paranoia Thinking abnormal
	Not known	Drug dependence
Nervous system disorders	Very common	Headache
	Common	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor
	Not known	Seizures
Eye disorders	Common	Lacrimal disorder Mydriasis

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Cardiac disorders	Common	Palpitations
Vascular disorders	Common	Vasodilatation
Respiratory, thoracic and mediastinal disorders	Common	Cough Dyspnoea Yawning
Gastrointestinal disorders	Very common	Nausea
	Common	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Gastrointestinal disorder Flatulence Tooth disorder Vomiting
Skin and subcutaneous tissue disorders	Very common	Hyperhidrosis
	Common	Rash
Musculoskeletal, connective tissue and bone disorders	Common	Arthralgia Back pain Bone pain Muscle spasms Myalgia Neck pain
Reproductive system and breast disorders	Common	Dysmenorrhoea
General disorders and administration site conditions	Very common	Drug withdrawal syndrome Pain

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	Common	Asthenia Chest pain Chills Malaise Oedema peripheral Pyrexia

Post-marketing data

Table 2 lists the most commonly reported adverse drug reactions reported during post-marketing surveillance. Events occurring in at least 1 % of reports by healthcare professionals and considered at least possibly related to treatment are included. Adverse drug reactions are presented by MedDRA System, Organ, Class in internationally agreed order by preferred term and frequency of reporting.

Table 2:	**Spontaneous adverse drug reactions collected through post-marketing surveillance reported by body system**
System Organ Class	**Preferred term**
Psychiatric disorders	Drug dependence
Nervous system disorders	Headache
Gastrointestinal disorders	Nausea Vomiting
General disorders and administration site conditions	Drug withdrawal syndrome Drug withdrawal syndrome neonatal Oedema peripheral

c. Description of selected adverse reactions

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

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- In cases of drug abuse or intentional drug misuse, some adverse experiences attributed to the act of misuse rather than the medicinal product have included: local reactions, such as cellulitis or abscess that are sometimes septic, potentially serious acute hepatitis, pneumonia, endocarditis and other serious infections (see section 4.4).
- Respiratory depression has occurred. Death due to respiratory depression has been reported, particularly when buprenorphine products were 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 CNS depressants such as alcohol or other opioids (see sections 4.4 and 4.5).
- Hypersensitivity reactions such as angioedema, or anaphylactic shock have occurred (see section 4.3).
- Transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy, hepatic necrosis have occurred (see section 4.4).
- Neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine products during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (see section 4.6).
- Hallucination, orthostatic hypotension, urinary retention, and vertigo have been reported (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com.

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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.

In the event of overdose, the cardiac and respiratory status of the patient should be monitored closely and appropriate supportive measures used. 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.

Treatment: 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 SUBLINGUAL should be taken into consideration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicines used in opioid dependence, ATC code: N07BC51.

Buprenorphine is an opioid partial agonist/antagonist which attaches itself to the μ (mu) and K (kappa) receptors of the brain.

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.
Peak plasma concentrations are achieved 90-360 minutes after sublingual administration.

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

Metabolism and elimination: Buprenorphine is metabolized by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite.
The N-dealkylbuprenorphine is a μ-agonist with weak intrinsic activity. Pre-clinical data suggest the CYP3A4 is responsible for the N-dealkylation of buprenorphine.
Elimination of buprenorphine is bi or triexponential, 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 faeces by biliary excretion of the glucuroconjugated metabolites (80 %), the rest being eliminated in the urine.

Hepatic impairment: Table 3 summarizes the results from a clinical trial in which the exposure of buprenorphine was determined after administering a buprenorphine/naloxone 2 mg/0,5 mg sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 3. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following buprenorphine/naloxone administration (change relative to health subjects)

PK Parameter	**Mild Hepatic Impairment (Child-Pugh Class A) (n=9)**	**Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)**	**Severe Hepatic Impairment (Child-Pugh Class C) (n=8)**
Buprenorphine			
C_{max}	1,2-fold increase	1,1-fold Increase	1,7-fold increase
AUC_{last}	Similar to control	1,6-fold increase	2,8-fold increase

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

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, mannitol, maize starch, povidone, citric acid, sodium citrate and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in a dry place.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

SUBUTEX SUBLINGUAL 0,4 mg, 2 mg and 8 mg tablets are packed in blister packs containing 7 or 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road, Aeroton,

Johannesburg, 2013

Tel: +27 11 494 8000

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8. REGISTRATION NUMBER(S)

SUBUTEX SUBLINGUAL 0,4 mg tablets: 33/34/0377

SUBUTEX SUBLINGUAL 2 mg tablets: 33/34/0378

SUBUTEX SUBLINGUAL 8 mg tablets: 33/34/0379

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

15 November 2002

10. DATE OF REVISION OF THE TEXT

27 July 2022

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