SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Prefibin 8 mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8 mg of buprenorphine (as hydrochloride).
Excipient(s) with known effect:
Each 8 mg sublingual tablet contains 278.1 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet.

White to off-white, oval tablet with a breaking notch on both sides (13.5 mm x 6.6 mm).

The 2 mg and 8 mg tablets can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment is intended for use in adults and adolescents aged 15 years and over who have agreed to be treated for addiction.

4.2 Posology and method of administration

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

The result of the treatment depends on the dose prescribed as well as on the combined medical, psychological, social and educational measures taken in monitoring the patient

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.

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy.
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 buprenorphine should be undertaken when objective and clear signs of withdrawal are evident (demonstrated e.g. by a score indicating mild to moderate withdrawal on the validated Clinical Opioid Withdrawal Scale, COWS).

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

- 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 buprenorphine therapy, the dose of methadone should be reduced to a maximum of 30 mg/day. Buprenorphine 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.

Dose adjustment and maintenance
The dose of buprenorphine should be increased progressively according to the clinical effect of the individual patient.

The mean maintenance daily dose is 8 mg. The majority of patients will not require doses exceeding 16 mg/day, however, the efficacy and safety of buprenorphine sublingual tablets was tested in clinical trials in doses up to 24 mg per day.

The dose is titrated according to reassessment of the clinical and psychological status of the patient and should not exceed a maximum single daily dose of 24 mg buprenorphine.

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

Dose reduction and termination of treatment
After a satisfactory period of stabilisation has been achieved, the dose 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 2 mg (divisible into 2x1 mg) and 8 mg (divisible into 2x4 mg), respectively, allows for a downward titration of dose. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

<u>Special populations</u>
Elderly
The safety and efficacy of buprenorphine in elderly patients over 65 years 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 in patients with severe renal impairment (creatinine clearance < 30 ml/min), which may require dose adjustment (see section 5.2).

Paediatric population

No data are available in children less than 15 years of age; therefore, buprenorphine is contraindicated in children under the age of 15 (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 medicinal product. The sublingual tablet should be kept under the tongue until dissolved, which usually occurs within 5 to 10 minutes.

Treatment goals and discontinuation
Before initiating treatment with Prefibin, 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 Prefibin, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Children and adolescents less than 15 years of age
- Severe respiratory insufficiency
- Severe hepatic insufficiency
- Acute alcoholism or delirium tremens
- Breast-feeding (see section 4.6)

4.4 Special warnings and precautions for use

Prefibin is 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 patients.

Misuse, abuse and diversion
Buprenorphine can be misused or abused in a manner similar to other opioids, legal or illicit. Some risks of misuse and abuse include overdose, spread of blood borne viral or localised 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.

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 below and 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, gabapentinoids (such as pregabalin and gabapentin) (see section 4.5) 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. Buprenorphine sublingual tablets 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, gabapentinoids or hypnotics) (see below and 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 medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe buprenorphine concomitantly with sedative medicinal products 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 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)
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as Prefibin. Abuse or intentional misuse of Prefibin 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 Prefibin 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.

Dependence
Buprenorphine is a partial agonist at the μ-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.

- 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 medicinal products and ongoing

injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing buprenorphine and during treatment. When a hepatic event is suspected further biological and etiological evaluation is required. Depending on 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 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 buprenorphine sublingual tablets, 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 metabolised 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. Buprenorphine 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 (see section 4.3).

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 when dosing patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 5.2).

QT prolongation
Caution should be exercised when co-administering buprenorphine sublingual tablets with other medicinal products that prolong the QT interval and in patients with a history of long QT syndrome or other risk factors for QT prolongation.

Use in adolescents
Due to lack of data in adolescents (age 15 – 18 years), 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.

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 dose.

Athletes must be aware that this medicinal product may cause a positive reaction to sports doping control tests. Use of buprenorphine as a doping agent may become a health hazard.

Buprenorphine contains lactose and sodium. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per sublingual tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Combination that is not recommended

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

Combinations where increased caution is required

- *Sedative medicinal products such as benzodiazepines or related medicinal products*
  The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products increases the risk of sedation,

respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4). These combinations must be avoided in cases where there is a risk of misuse.

- *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.
- *Gabapentinoids:* The concomitant use of buprenorphine with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death. This combination may result in death due to respiratory depression of central origin. Therefore, doses must be closely monitored and this combination must be avoided in cases where there is a risk of misuse. Patients should be cautioned to use gabapentinoids (such as pregabalin and gabapentin) concurrently with this medicinal product only as directed by their physician (see section 4.4).
- *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.
- *Anticholinergics or medications with anticholinergic activity:* 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.
- *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.
- *CYP3A4 inhibitors:* An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (approximately 50% and 70%, respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving buprenorphine sublingual tablets 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 buprenorphine should be closely monitored if enzyme 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

- *Monoamine oxidase inhibitors (MAOI):* Possible exacerbation of the effects of opioids, based on experience with morphine.
- *Serotonergic medicinal products*: 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).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of buprenorphine in pregnent 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 causea 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 is contra-indicated and must be discontinued during treatment with Prefibin (see section 4.3).

Fertility
No human data on fertility are available. There were no adverse effects on fertility or general reproductive function in rats, although at the highest intramuscular dose (5 mg/kg/day) the mothers experienced some difficulty in parturition and there was a high neonatal mortality (see section 5.3).

4.7 Effects on ability to drive and use machines

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:

o The medicine has been prescribed to treat a medical or dental problem and
o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
o It was not affecting your ability to drive safely.

Buprenorphine has moderate influence on the ability to use machines when administered to opioid dependent patients. Buprenorphine 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 aboutoperating hazardous machinery in case buprenorphine may affect their ability to engage in such activities.

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 summarises:
adverse reactions reported from pivotal clinical studies.
The frequency of possible side effects listed below is based on the following convention:
very common (≥ 1/10) ; common (≥ 1/100 to <1/10) ; uncommon (≥ 1/1,000 to <1/100)

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	Common	Uncommon	Frequency not known
Infections and infestations		Bronchitis, Infection, Influenza, pharyngitis, rhinitis		
Blood and lymphatic system disorders		Lymphadenopathy		
Immune system disorders				Anaphylactic shock, angioedema

Table 1: Adverse effects observed in pivotal clinical studies and / or post marketing surveillance listed by body system				
System Organ Class	**Very common**	**Common**	**Uncommon**	**Frequency not known**
Metabolism and nutrition disorders		Decreased appetite		
Psychiatric disorders	Insomnia	Agitation, anxiety, depression, hostility, nervousness, paranoia, thinking abnormal	Hallucination	Drug dependence
Nervous system disorders	Headache	Dizziness, hypertonia, migraine, paraesthesia, somnolence, syncope, tremor		Vertigo
Eye disorders		Lacrimation disorders, mydriasis		
Cardiac disorders		Palpitations		
Vascular disorders		Vasodilatation orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Cough, dyspnoea, yawning	Respiratory depression	Bronchospasm
Gastrointestinal disorders	Nausea	Abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, gastrointestinal disorders, flatulence, tooth disorder, vomiting,		Dental caries

Table 1: Adverse effects observed in pivotal clinical studies and / or post marketing surveillance listed by body system				
System Organ Class	**Very common**	**Common**	**Uncommon**	**Frequency not known**
Hepatobiliary disorders			Hepatic necrosis, hepatitis	
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash		
Musculoskeletal and connective tissue disorders		Arthralgia, back pain, bone pain muscle spasms, myalgia, neck pain		
Reproductive system and breast disorders		Dysmenorrhoea		
Renal and urinary disorders				Urinary retention
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 drug withdrawal syndrome 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, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy 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).

- Drug dependence: Repeated use of Prefibin 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).

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: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store.

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
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

Pharmacotherapeutic group: Other nervous system drugs, Drugs used in opioid dependence
ATC code: N07 BC01

Mechanism of action

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 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 glucuroconjugation in the small intestine and in the liver. The use of this medicinal product by the oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration 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 glucuroconjugation of the parent molecule and the dealkylated metabolite. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity.

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 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 post-marketing study.

Table 2 summarises the results from a clinical trial in which the exposure of buprenorphine was determined after administering a buprenorphine/naloxone 2.0 mg/0.5mg 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 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.

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.

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 on fertility or general reproductive function in rats, although at the highest intramuscular dose (5 mg/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 75 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous
Lactose monohydrate
Mannitol
Sodium citrate
Sodium stearyl fumarate
Pregelatinised starch (maize)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister packs

Pack sizes 7, 10, 20, 24, 28, 30, 48 or 50 sublingual tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Maxis 1

Western Road
Bracknell
United Kingdom
RG12 1RF

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0949

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/09/2011

10 DATE OF REVISION OF THE TEXT

03/07/2025