SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buprenorphine 2 mg Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.16 mg of buprenorphine hydrochloride (equivalent to 2 mg of buprenorphine).

Excipient(s) with known effect

Each tablet contains 16.25 mg of lactose monohydrate and 0.056 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual Tablet

White to off-white, oval shaped, approximately 7.5 x 4 mm, biconvex uncoated tablet debossed with ‘B’ and ‘2’ separated with breakline on one side and plain surface on the other side.

The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with buprenorphine in order to minimize 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 Buprenorphine sublingual tablets is intended for use in adults and children aged 16 years or over who have agreed to be treated for opioid dependence.

Precautions to be taken before dosing

Prior to treatment induction, physicians should be aware of the partial agonist profile of buprenorphine to the opiate receptors, which may precipitate a withdrawal syndrome in opioid-dependent patients and consideration should be given to the types of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with Buprenorphine should be undertaken when objective and clear signs of withdrawal are evident e.g. a score higher than 12 on the Clinical Opioid Withdrawal Scale (COWS).

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

- **For patients receiving methadone:** before beginning Buprenorphine therapy, the dose of methadone should be reduced to a maximum of 30mg/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.

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

Induction:

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

Dosage adjustment and maintenance:

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

Dosage reduction and termination of treatment:

After a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose; when deemed appropriate, treatment may be discontinued in some patients. The availability of the sublingual tablet in doses of 0.4mg, 2mg and 8mg, respectively, allows for a downward titration of dosage. Patients should be monitored following termination of buprenorphine treatment because of the potential for relapse.

Special populations

Elderly

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

Hepatic impairment

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

Renal impairment

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

Paediatric population

Buprenorphine is contraindicated in children under the age of 16 (see section 4.3).

Method of administration

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

Treatment goals and discontinuation

Before initiating treatment with buprenorphine, a treatment strategy including treatment duration and treatment goals, should be agreed together with the patient. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with buprenorphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Children less than 16 years of age

Severe respiratory insufficiency

Severe hepatic insufficiency

Acute alcoholism or delirium tremens

Breast feeding

4.4 Special warnings and precautions for use

Buprenorphine 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).

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 buprenorphine. Abuse or intentional misuse of buprenorphine may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history

(parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with buprenorphine and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2).

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and psychoactive drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

Seizures

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

Respiratory depression

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

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

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

CNS depression

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

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

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

Serotonin syndrome

Concomitant administration of buprenorphine and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

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

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

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.

Hepatitis and hepatic events

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

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

Drug withdrawal syndrome

Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with buprenorphine. The decision to maintain a patient on a long-term opioid prescription should be an active decision agreed between the clinician and patient with review at regular intervals (usually at least three-monthly, depending on clinical progress).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their new-born infants will experience neonatal withdrawal syndrome.

Precipitation of opioid withdrawal syndrome

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

Hepatic impairment

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study. Buprenorphine is extensively metabolized in the liver, plasma levels were found to be higher for buprenorphine in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of buprenorphine. 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.

Renal impairment

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

Use in adolescents

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

General warnings related to the administration of opioids

Opioids may cause orthostatic hypotension in ambulatory patients.

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

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

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

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

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

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

Excipients

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Buprenorphine should not be taken together with:

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

Buprenorphine should be used cautiously together with:

- sedatives such as benzodiazepines or related medicinal products: The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The concomitant use of buprenorphine with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4). The dose and duration of concomitant use of sedative medicines should be limited (see section 4.4). Patients should be warned that it is extremely dangerous to self administer non-prescribed benzodiazepines whilst taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed (see section 4.4).

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

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

- other central nervous system depressants: Other opioid derivatives (e.g. methadone, analgesics and antitussives); certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. These combinations increase central nervous system depression. The reduced level of alertness can make driving and using machinery hazardous.

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Towards the end of pregnancy, buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration during the last three months of pregnancy may cause a withdrawal syndrome in the neonate (e.g. hypertonia, neonatal tremor, neonatal agitation,

myoclonus or convulsions). The syndrome is generally delayed from several hours to several days after birth.

Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Breast feeding

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

4.7 Effects on ability to drive and use machines

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

This medicine can impair cognitive function and can affect a patient's ability to drive safely.

This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

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

4.8 Undesirable effects

Summary of safety profile

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

Tabulated list of adverse reactions

Table 1 summarises:

- adverse reactions reported from pivotal clinical studies. The frequency of possible side effects listed below is defined using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), not known (cannot be estimated from the available data).

- the most commonly reported adverse drug reactions during post-marketing surveillance. Events occurring in at least 1% of reports by healthcare professionals and considered expected are included. Frequency of events not reported in pivotal studies cannot be estimated and is given as not known.

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

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

Psychiatric disorders	Insomnia	Agitation Anxiety Depression Hostility Nervousness Paranoia Thinking abnormal	Drug dependence (see section 4.4)
Nervous system disorders	Headache	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor	Seizures
Eye disorders		Lacrimal disorder Mydriasis	
Cardiac disorders		Palpitations	
Vascular disorders		Vasodilatation	
Respiratory, thoracic and mediastinal disorders		Cough Dyspnoea Yawning	
Gastrointestinal disorders	Nausea	Abdominal pain	

		Constipation Diarrhoea Dry mouth Dyspepsia Gastrointestinal disorder Flatulence Tooth disorder Vomiting	
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash	
Musculoskeletal, connective tissue and bone disorders		Arthralgia Back pain Bone pain Muscle spasms Myalgia Neck pain	
Reproductive system and breast disorders		Dysmenorrhoea	
General disorders and administration site conditions	Drug withdrawal syndrome Pain	Asthenia Chest pain Chills Malaise Oedema peripheral	Drug withdrawal syndrome neonatal

		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.

Drug dependence
Repeated use of buprenorphine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

Symptoms

Respiratory depression, as a result of central nervous system depression, is the primary symptom requiring intervention in the case of overdose because it may lead to respiratory arrest and death. Preliminary symptoms of overdose may also include somnolence, amblyopia, miosis, hypotension, nausea, vomiting and / or speech disorders.

Treatment

General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, following standard intensive care measures, should be instituted. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available. Use of an opioid antagonist (i.e., naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic group

Drugs used in opioid dependence ATC-code: N07BC01

Mechanism of action

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

Clinical efficacy and safety

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

5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

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

Biotransformation and elimination

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

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

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

<u>Hepatic Impairment</u>

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

Table 2 summarizes the results from a clinical trial in which the exposure of buprenorphine was determined after administering a buprenorphine/naloxone 2.0/0.5mg 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 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 (LD50) in the mouse were 26, 94 and 261 mg/kg for intravenous, intraperitoneal and oral administration, respectively. The LD50 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 (5mg/kg/day) the mothers experienced some difficulty in parturition and there was a high neonatal mortality.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol
Starch, pregelatinised (maize starch)
Citric acid
Sodium citrate
Povidone (k-30)
Sodium stearyl fumarate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The sublingual tablets packed in blister packs (i.e. clear PVC/PVdC- paper/ polyester/aluminium foil (peelable foil)) containing 7 tablets

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Milpharm Limited
Ares Block,
Odyssey Business Park,
West End Road,
Ruislip, HA4 6QD
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 16363/0739

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/12/2023

10 DATE OF REVISION OF THE TEXT

13/09/2024