

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Buprenorphine 2 mg Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of buprenorphine (as buprenorphine hydrochloride).

Excipient: Each tablet contains 20 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet.

Off-white to brownish, oval, biplane tablets marked with "B2" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

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

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

Dosage reduction and termination of treatment:

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

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with buprenorphine in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Special populations**Elderly**

The safety and efficacy of buprenorphine in elderly patients over 65 years of age have 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 Sublingual Tablets are contraindicated in children under the age of 16 (see section 4.3).

Method of administration

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

4.3 Contraindications

- Hypersensitivity to buprenorphine or any of the excipients
- Children and adolescents 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 that treatment is prescribed by a physician who ensures comprehensive management of the opioid-dependent patient(s)

Misuse, abuse and diversion

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

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 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.

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 in opioid-dependent patients particularly 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).

Patient with lactose intolerance

This medicinal product contains lactose (See section 6.1). Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or 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'.

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 can 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.

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.

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

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g. major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

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 analgesic treatment should be reviewed regularly.

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.

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. Tapering from a high dose may take weeks to months.

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.

Hyperalgesia

Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

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.

4.5 Interaction with other medicinal products and other forms of interactions

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 when co-administered with:

- **Benzodiazepines:** This combination may result in death due to respiratory depression of central origin, therefore, patients must be closely monitored and this combination should be avoided where there is the risk of misuse. 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).
- **Other central nervous system depressants; other opioid derivatives (methadone, analgesics and antitussives); certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances.** This combination increases 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.
- **CYP3A4 inhibitors:** An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving 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, orazole 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. therefore, it is recommended that patients receiving buprenorphine should be closely monitored if enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. The dose of either buprenorphine or the CYP3A4 inducer may need to be adjusted.

- **Monoamine oxidase inhibitors (MAOI):** Possible exacerbation of the effects of opioids, based on experience with morphine.
- **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 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 new born infants. even after a short period of administration. Long-term administration during the last three months of pregnancy, may cause withdrawal syndrome in neonates (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.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breast-feeding

Buprenorphine and its metabolites are excreted in human breast milk. As evidenced in rats, buprenorphine been found to inhibit lactation.

Administration to nursing women is not recommended as buprenorphine may be secreted in breast milk and may cause respiratory depression in the infant.

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).
- 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.

<u>Adverse effects observed in pivotal clinical studies and / or post marketing surveillance listed by body system</u>			
<i>System Organ Class</i>	Very common (≥1/10)	Common (≥1/100 to <1/10)	Frequency not known
<i>Infections and infestations</i>		Bronchitis Infection Influenza Pharyngitis Rhinitis	
<i>Blood and lymphatic system disorders</i>		Lymphadenopathy	
<i>Metabolism and nutrition disorders</i>		Decreased appetite	
<i>Psychiatric disorders</i>	Insomnia	Agitation Anxiety Depression Hostility Nervousness Paranoia Thinking abnormal	Drug dependence (see section 4.4)
<i>Nervous system disorders</i>	Headache	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor	Seizures
<i>Eye disorders</i>		Lacrimal disorder Mydriasis	
<i>Cardiac disorders</i>		Palpitations	
<i>Vascular disorders</i>		Vasodilatation	
<i>Respiratory, thoracic and mediastinal disorders</i>		Cough Dyspnoea Yawning	
<i>Gastrointestinal disorders</i>	Nausea	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Gastrointestinal disorder Flatulence Tooth disorder Vomiting	
<i>Skin and subcutaneous tissue disorders</i>	Hyperhidrosis	Rash	
<i>Musculoskeletal, connective tissue and bone disorders</i>		Arthralgia Back pain Bone pain Muscle spasms Myalgia Neck pain	
<i>Reproductive system and breast disorders</i>		Dysmenorrhoea	

<i>General disorders and administration site conditions</i>	Drug withdrawal syndrome Pain	Asthenia Chest pain Chills Malaise Oedema peripheral Pyrexia	Drug withdrawal syndrome neonatal
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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
- 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 new borns of women who have received buprenorphine during pregnancy. The syndrome may be milder than that seen with a full μ -opioid agonist and may be delayed in onset. The nature of the syndrome may vary depending upon the mother's drug use history (see section 4.6).
- Hallucination, orthostatic hypotension, urinary retention and vertigo have been reported

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

Respiratory depression as a result of central nervous system depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus. 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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 propertiesAbsorption

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

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

Distribution

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

Biotransformation and elimination

Buprenorphine is 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 summarizes the results from a clinical trial in which the exposure of buprenorphine and naloxone 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			
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 (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 (E421)
Maize starch
Citric acid, anhydrous
Sodium citrate
Povidone (Plasdone K29/32)
Magnesium stearate
Ascorbic acid
Edetic acid (EDTA)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

White opaque PVC/PVDC/Aluminium foil blisters with 7 tablets per blister.
Pack sizes: 7, 14, or 28 tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare (Malta) Limited
93 Mill Street
Qormi QRM 3102
Malta

8 MARKETING AUTHORISATION NUMBER

PA23142/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 September 2010

Date of last renewal: 18th March 2012

10 DATE OF REVISION OF THE TEXT

October 2021