Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bulexin 4 mg/1 mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bulexin 4 mg/1 mg sublingual tablets
Each sublingual tablet contains 4 mg buprenorphine (as hydrochloride) and 1 mg naloxone (as hydrochloride dihydrate).

Excipient(s) with known effect:
Each sublingual tablet contains 79.80 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Buprenorphine/Naloxone Pinewood 4 mg/1 mg
White to off-white, round and biconvex tablets, with score line on one side and a diameter of about 8.5 mm.
The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. The intention of the naloxone component is to deter intravenous misuse.
Treatment is intended for use in adults and adolescents over 15 years of age 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.

Precautions to be taken before induction
Prior to treatment initiation, consideration should be given to the type 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/naloxone or buprenorphine only 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).

- For patients dependent upon heroin or short-acting opioids, the first dose of buprenorphine/naloxone should be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.
- For patients receiving methadone, the dose of methadone should be reduced to a maximum of 30 mg/day before beginning buprenorphine/naloxone therapy. The long half-life of methadone should be considered when starting buprenorphine/naloxone. The first dose of buprenorphine/naloxone should be taken only when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

Posology

Initiation therapy (induction)
The recommended starting dose in adults and adolescents over 15 years of age is. 4 mg/1 mg and can be repeated up to a maximum dose of 12 mg/ 3 mg on day 1 to minimise undue withdrawal symptoms and retain the patient in treatment.

During the initiation of treatment, daily supervision of dosing is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.

Dosage adjustment and maintenance therapy
Following treatment induction on day one, the patient should be stabilised to a maintenance dose during the next few days by progressively adjusting the dose according to the clinical effect of the individual patient. Dose titration in steps of 2-8 mg buprenorphine is guided by 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 buprenorphine may be given 16 mg buprenorphine 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 buprenorphine. Patients requiring a titrated daily dose > 8 mg buprenorphine/day may not find this regimen adequate.

Medical withdrawal
After a satisfactory stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of doses of 2 mg/0.5 mg and 8 mg/2 mg allows for a downward titration of dosage. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg may be used. Patients should be monitored following medical withdrawal because of the potential for relapse.

Switching between buprenorphine and buprenorphine/naloxone
When used sublingually, buprenorphine/naloxone and buprenorphine have similar clinical effects and are interchangeable; however, before switching between buprenorphine/naloxone and buprenorphine, the prescriber and patient should agree to the change, and the patient should be monitored in case a need to readjust the dose occurs.

Special populations

Elderly
The safety and efficacy of buprenorphine/naloxone in elderly patients over 65 years of age have not been established. No recommendation on posology can be made.

Hepatic impairment
As buprenorphine/naloxone pharmacokinetics may be altered in patients with hepatic impairment, lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended. Buprenorphine/naloxone is contraindicated in patients with severe hepatic impairment. (see section 4.3 and 5.2).

Renal impairment
Modification of the buprenorphine/naloxone dose is not required in patients with renal impairment. Caution is recommended when dosing patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4 and 5.2).

Paediatric population
The safety and efficacy of buprenorphine/naloxone in children and adolescents below the age of 15 years have not been established. No data are available.

Method of administration
Physicians must warn patients that the sublingual route is the only effective and safe route of administration for this medicinal product (see section 4.4). The tablet is to be placed under the tongue until completely dissolved. Patients should not swallow or consume food or drink until the tablet is completely dissolved.
The dose is made up from multiple Bulexin tablets of different strengths, which may be taken all at the same time or in two divided portions; the second portion to be taken directly after the first portion has dissolved.

4.3 Contraindications

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

Severe respiratory insufficiency
Severe hepatic impairment
Acute alcoholism or *delirium tremens*.
Concomitant administration of opioid antagonists (naltrexone, nalmefene) for the treatment of alcohol or opioid dependence.

4.4 Special warnings and precautions for use

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 and systemic 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 medicinal product is distributed for illicit use directly by the intended patient or if the medicinal product is not safeguarded against theft.
Sub-optimal treatment with buprenorphine/naloxone may prompt medicinal product misuse by the patient, leading to overdose or treatment dropout. A patient who is under-dosed with buprenorphine/naloxone may continue responding to uncontrolled withdrawal symptoms by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.
To minimize the risk of misuse, abuse and diversion, physicians should take appropriate precautions when prescribing and dispensing buprenorphine, such as to avoid prescribing multiple refills early in treatment, and to conduct patient follow-up visits with clinical monitoring that is appropriate to the patient's needs.
Combining buprenorphine with naloxone in Bulexin is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of Bulexin is expected to be less likely than buprenorphine alone since the naloxone in Bulexin can precipitate withdrawal in individuals dependent on heroin, methadone, or other opioid agonists.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Bulexin 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 Bulexin concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.
The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

The risk for respiratory depression also exists when buprenorphine is 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.
This product should be used with care in patients with asthma or respiratory insufficiency (e.g. chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, pre-existing respiratory depression or kyphoscoliosis (curvature of spine leading to potential shortness of breath)).
Buprenorphine/naloxone may cause severe, possibly fatal, respiratory depression in children and non-dependent persons in case of accidental or deliberate ingestion. Patients must be warned to store the blister safely, to never open the blister in advance, to keep them out of the reach of children and other household members, and not to take this medicinal product in front of children. An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

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.

CNS depression
Buprenorphine/naloxone may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants (such as benzodiazepines, tranquilisers, sedatives or hypnotics) (see section 4.5 and 4.7).

Serotonin syndrome
Concomitant administration of Bulexin 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 μ (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 e.g. morphine.
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 addicts both in clinical trials and in post marketing adverse reaction reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases the presence of pre-existing mitochondrial impairment (genetic disease, liver enzyme abnormalities, 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/naloxone and during treatment. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.

Precipitation of opioid withdrawal syndrome
When initiating treatment with buprenorphine/naloxone, the physician must be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients, particularly if administered less than 6 hours after the last use of heroin or other short-acting opioid, or if administered less than 24 hours after the last dose of methadone. Patients should be clearly monitored during the switching period from buprenorphine or methadone to buprenorphine/naloxone since withdrawal symptoms have been reported. To avoid precipitating withdrawal, induction with buprenorphine/naloxone should be undertaken when objective signs of withdrawal are evident (see section 4.2).
Withdrawal symptoms may also be associated with sub-optimal dosing.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Since both buprenorphine and naloxone are extensively metabolized, plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment after single-dose administration. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine. Bulexin 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/naloxone is contraindicated.

Baseline liver function tests and documentation of viral hepatitis status is recommended prior to commencing therapy. Patients who are positive for viral hepatitis, on concomitant medicinal products (see section 4.5) and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Both active substances of Bulexin, buprenorphine and naloxone, are extensively metabolized in the liver, and the plasma levels were found to be higher for both buprenorphine and naloxone 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 naloxone and/or buprenorphine.

Renal impairment
Renal elimination may be prolonged since 30% of the administered dose is eliminated by the renal route. 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 sections 4.2 and 5.2).

Use in adolescents (Age 15≤18)
Due to the lack of data in adolescents (age 15≤18), patients in this age group should be more closely monitored during treatment.

CYP 3A inhibitors
Medicinal products that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the buprenorphine/naloxone dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of buprenorphine/naloxone titrated carefully since a reduced dose may be sufficient in these patients (see section 4.5).

General warnings relevant to the administration of opioids
Opioids may produce orthostatic hypotension in ambulatory patients.
Opioids may elevate cerebrospinal fluid pressure, which may cause seizures, so opioids should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or history of seizure.
Opioids should be used with caution in patients with hypotension, prostatic hypertrophy or urethral stenosis.
Opioid-induced miosis, changes in the level of consciousness, or changes in the perception of pain as a symptom of disease may interfere with patient evaluation or obscure the diagnosis or clinical course of concomitant disease.
Opioids should be used with caution in patients with myxoedema, hypothyroidism, or adrenal cortical insufficiency (e.g., Addison's disease).
Opioids have been shown to increase intracholedochal pressure, and should be used with caution in patients with dysfunction of the biliary tract.
Opioids should be administered with caution to elderly or debilitated patients.
The concomitant use of monoamine oxidase inhibitors (MAOI) might produce an exaggeration of the effects of opioids, based on experience with morphine (see section 4.5).

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

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

Bulexin may cause a positive reaction in tests conducted during anti-doping checks.
Please note that Bulexin contains buprenorphine, which may give positive results in a doping test.

4.5 Interaction with other medicinal products and other forms of interaction

Bulexin should not be taken together with:
• alcoholic drinks or medicinal products containing alcohol, as alcohol increases the sedative effect of buprenorphine (see section 4.7).

Bulexin should be used cautiously when co-administered with:

- Sedative medicines such as benzodiazepines or related drugs: 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 dose and duration of concomitant use should be limited (see section 4.4). Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking this product, and should also be cautioned to use benzodiazepines concurrently with this product only as directed by their physician (see section 4.4).

- 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 machines hazardous.

- Furthermore, adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine/naloxone. Therefore the potential to overdose with a full agonist exists, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.

- Naltrexone and nalmefene are opioid antagonists that can block the pharmacological effects of buprenorphine. Co-administration during buprenorphine/naloxone treatment is contraindicated due to the potentially dangerous interaction that may precipitate a sudden onset of prolonged and intense opioid withdrawal symptoms (see section 4.3).

- CYP3A4 inhibitors: an interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased $C_{max}$and AUC (area under the curve) of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving Bulexin 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 or itraconazole, 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/naloxone should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. The dose of buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

- The concomitant use of monoamine oxidase inhibitors (MAOI) might produce exaggeration 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 limited data from the use of Bulexin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Towards the end of pregnancy buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration of buprenorphine 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 for several hours to several days after birth.
Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy, to prevent the risk of respiratory depression or withdrawal syndrome in neonates.
Furthermore, the use of buprenorphine/naloxone during pregnancy should be assessed by the physician.
Buprenorphine/naloxone should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Breastfeeding
It is unknown whether naloxone is excreted in human breast milk. Buprenorphine and its metabolites are excreted in human breast milk. In rats buprenorphine has been found to inhibit lactation. Therefore, breastfeeding should be discontinued during treatment with Bulexin.

Fertility
Animal studies have shown a reduction in female fertility at high doses (systemic exposure > 2.4 times the human exposure at the maximum recommended dose of 24 mg buprenorphine, based on AUC). See section 5.3.

4.7 Effects on ability to drive and use machines

Buprenorphine/naloxone has minor to moderate influence on the ability to drive and use machines when administered to opioid dependent patients. This medicinal product 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 sections 4.4 and 4.5).
Patients should be cautioned about driving or operating hazardous machinery in case buprenorphine/naloxone may affect their ability to engage in such activities.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported treatment related adverse reactions reported during the pivotal clinical trials were constipation and symptoms commonly associated with drug withdrawal (i.e. insomnia, headache, nausea, hyperhidrosis and pain). Some reports of seizure, vomiting, diarrhoea, and elevated liver function tests were considered serious.

Tabulated list of adverse reactions
Table 1 summarises adverse reactions reported from pivotal clinical trials in which, 342 of 472 patients (72.5%) reported adverse reactions and adverse reactions reported during post-marketing surveillance.

The frequency of possible undesirable effects listed below is defined using the following convention:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Not known (cannot be estimated from available data).

Table 1: Treatment-related adverse reactions reported in clinical trials and post-marketing surveillance of buprenorphine/naloxone

System Organ Class	Very common	Common	Uncommon	Not known
Infections and infestations		Influenza Infection Pharyngitis Rhinitis	Urinary tract infection Vaginal infection	
Blood and lymphatic system disorders			Anaemia Leukocytosis Leukopenia Lymphadenopathy Thrombocytopenia	
Immune system disorders			Hypersensitivity	Anaphylactic shock
Metabolism and nutrition disorders			Decreased appetite Hyperglycaemia Hyperlipidaemia Hypoglycaemia	
Psychiatric disorders	Insomnia	Anxiety Depression Libido decreased Nervousness Thinking abnormal	Abnormal dreams Agitation Apathy Depersonalisation Drug dependence Euphoric mood Hostility	Hallucination
Nervous system disorders	Headache	Migraine Dizziness Hypertonia	Amnesia Hyperkinesia Seizure	Hepatic encephalopathy Syncope

		Paraesthesia Somnolence	Speech disorder Tremor	
Eye disorders		Amblyopia Lacrimal disorder	Conjunctivitis Miosis	
Ear and labyrinth disorders				Vertigo
Cardiac disorders			Angina Pectoris Bradycardia Myocardial infarction Palpitations Tachycardia	
Vascular disorders		Hypertension Vasodilatation	Hypotension	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders		Cough	Asthma Dyspnoea Yawning	Bronchospasm Respiratory depression
Gastrointestinal disorders	Constipation Nausea	Abdominal Pain Diarrhoea Dyspepsia Flatulence Vomiting	Mouth ulceration Tongue discolouration	
Hepatobiliary disorders				Hepatitis Hepatitis acute Jaundice Hepatic necrosis Hepatorenal syndrome
Skin and subcutaneous tissue disorders	Hyperhidrosis	Pruritus Rash Urticaria	Acne Alopecia Dermatitis exfoliative Dry skin Skin mass	Angioedema
Musculoskeletal and connective tissue disorders		Back Pain Arthralgia Muscle spasms Myalgia	Arthritis	
Renal and urinary disorders		Urine Abnormality	Albuminuria Dysuria Haematuria Nephrolithiasis Urinary retention	
Reproductive system and breast disorders		Erectile dysfunction	Amenorrhoea Ejaculation disorder Menorrhagia Metrorrhagia	
General disorders and administration site conditions	Drug withdrawal syndrome	Asthenia Chest Pain Chills Pyrexia Malaise Pain Oedema peripheral	Hypothermia	Drug withdrawal syndrome neonatal (see section 4.6)
Investigations		Liver function test abnormal Weight	Blood creatinine increased	Transaminases increased

		decreased		
Injury, poisoning and procedural complications		Injury	Heat stroke	

Description of selected adverse reactions
In cases of intravenous drug misuse, some adverse experiences are attributed to the act of misuse rather than the medicinal product and include local reactions, sometimes septic (abscess, cellulitis), and potentially serious acute hepatitis, and other acute 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 (see sections 4.2 and 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 national reporting system listed below:

HPRA Pharmacovigilance
Website: www.hpra.ie

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

Management
General supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. Symptomatic treatment of respiratory depression, and standard intensive care measures, should be implemented. 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.
If the patient vomits, care must be taken to prevent aspiration of the vomitus.
Use of an opioid antagonist (i.e., naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.
If naloxone is used, the long duration of action of buprenorphine should be taken into consideration when determining the length of treatment and medical surveillance 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, so a continuing infusion may be necessary. If infusion is not possible, repeated dosing with naloxone may be required. Ongoing intravenous infusion rates should be titrated to patient response.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, drugs used in addictive disorders, ATC code: N07BC51.

Mechanism of action
Buprenorphine is an opioid partial agonist/antagonist which binds to the μ and κ (kappa) opioid receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the μ-opioid receptors which, over a prolonged period, might minimise the need of addicted patients for drugs.
Opioid agonist ceiling effects were observed during clinical pharmacology studies in opioid-dependent persons.

Naloxone is an antagonist at μ-opioid receptors. When administered orally or sublingually in usual doses to patients experiencing opioid withdrawal, naloxone exhibits little or no pharmacological effect because of its almost complete first pass metabolism. However, when administered intravenously to opioid-dependent persons, the presence of naloxone in Bulexin produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Clinical efficacy

Efficacy and safety data for buprenorphine/naloxone are primarily derived from a one-year clinical trial, comprising a 4-week randomised double blind comparison of buprenorphine/naloxone, buprenorphine and placebo followed by a 48 week safety study of buprenorphine/naloxone. In this trial, 326 heroin-addicted subjects were randomly assigned to either buprenorphine/naloxone 16 mg per day, 16 mg buprenorphine per day or placebo. For subjects randomized to either active treatment, dosing began with 8 mg of buprenorphine on Day 1, followed by 16 mg (two 8 mg) of buprenorphine on Day 2. On Day 3, those randomized to receive buprenorphine/naloxone were switched to the combination tablet. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. The primary study comparison was to assess the efficacy of buprenorphine and buprenorphine/naloxone individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both buprenorphine/naloxone versus placebo ($p < 0.0001$) and buprenorphine versus placebo ($p < 0.0001$).

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution to a full agonist active control, 162 subjects were randomized to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of buprenorphine/naloxone), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually. Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control, in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of buprenorphine, 8 mg per day was similar to that of the moderate active control dose, but equivalence was not demonstrated.

5.2 Pharmacokinetic properties

Buprenorphine

Absorption

Buprenorphine, when taken orally, undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and 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. Plasma levels of buprenorphine increased with the sublingual dose of buprenorphine/naloxone. Both C_{max} and AUC of buprenorphine increased with the increase in dose (in the range of 4-16 mg), although the increase was less than dose-proportional.

Table 2. Pharmacokinetic parameters of buprenorphine.

Pharmacokinetic Parameter	Bulexin 4 mg	Bulexin 8 mg	Bulexin 16 mg
C_{max} ng/ml	1.84 (39)	3.0 (51)	5.95 (38)
AUC_{0-48} hour ng/ml	12.52 (35)	20.22 (43)	34.89 (33)

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours). Buprenorphine is highly lipophilic, which leads to rapid penetration of the blood-brain barrier. Buprenorphine is approximately 96 % protein bound, primarily to alpha and beta globulin.

Biotransformation and elimination

Buprenorphine is primarily metabolised through N-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation. Norbuprenorphine binds to opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of buprenorphine/naloxone.

Elimination of buprenorphine is bi- or tri-exponential, and has a mean half-life from plasma of 32 hours.

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

Naloxone

Absorption and distribution

Naloxone mean peak plasma concentrations were too low to assess dose-proportionality, and in seven of eight subjects tested who had naloxone plasma levels above the limit of quantification (0.05 ng/mL), naloxone was not detected beyond 2 hours post-dose.

Naloxone has not been found to affect the pharmacokinetics of buprenorphine, and both buprenorphine sublingual tablets and buprenorphine/naloxone sublingual film deliver similar plasma concentrations of buprenorphine. Naloxone is approximately 45 % protein bound, primarily to albumin.

Biotransformation
The medicinal product is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as N-dealkylation and
reduction of the 6-oxo group. Naloxone is excreted in the urine, with a mean half-life of elimination from plasma ranging from 2 to 12 hours.

Special populations
Elderly
No pharmacokinetic data in elderly patients are available.
Renal impairment
Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine/naloxone. No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment (see Section 4.3).
Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study.

Table 3 summarizes the results from a clinical trial in which the exposure after single-dose administration of buprenorphine/naloxone 2.0/0.5mg sublingual tablet was determined in healthy subjects, and in subjects with hepatic impairment.

Table 3. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine and naloxone 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
Naloxone			
C_{max}	Similar to control	2.7-fold increase	11.3-fold increase
AUC_{last}	0.2-fold decrease	3.2-fold increase	14.0-fold increase

Overall, buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function, while naloxone plasma exposure increased 14-fold with severely impaired hepatic function.

5.3 Preclinical safety data

The combination of buprenorphine and naloxone has been investigated in acute and repeated dose (up to 90 days in rats) toxicity studies in animals. No synergistic enhancement of toxicity has been observed. Undesirable effects were based on the known pharmacological activity of opioid agonistic and/or antagonistic substances.
The combination (4:1) of buprenorphine hydrochloride and naloxone hydrochloride was not mutagenic in a bacterial mutation assay (Ames test), and was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an intravenous micronucleus test in the rat.
Reproduction studies by oral administration of buprenorphine: naloxone (ratio 1:1) indicated that embryolethality occurred in rats in the presence of maternal toxicity at all doses. The lowest dose studied represented exposure multiples of 1x for buprenorphine and 5x for naloxone at the maximum human therapeutic dose calculated on a mg/m^2 basis. No developmental toxicity was observed in rabbits at maternally toxic doses. Further, no teratogenicity has been observed in either rats or rabbits.
A peri-postnatal study has not been conducted with buprenorphine/naloxone; however, maternal oral administration of buprenorphine at high doses during gestation and lactation resulted in difficult parturition (possible as a result of the sedative effect of buprenorphine), high neonatal mortality and a slight delay in the development of some neurological functions (surface righting reflex and startle response) in neonatal rats.
Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (estimated exposure approximately 2.4x for buprenorphine at a human dose of 24 mg buprenorphine/naloxone based on AUC, plasma levels of naloxone were below the limit of detection in rats) had no adverse effect on fertility in females.
A carcinogenicity study with buprenorphine/naloxone was conducted in rats at doses of 7, 30 and 120 mg/kg/day, with estimated exposure multiples of 3 to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m^2 basis.

Statistically significant increases in the incidence of benign testicular interstitial (Leydig's) cell adenomas were observed in all dosage groups.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol
Maize starch
Povidone
Citric acid monohydrate
Sodium citrate
Magnesium stearate
Acesulfame potassium
Lemon flavour 01600158 (contains: lime oil, lime terepenes, lemon oil, maltodextrin, stabiliser E414)
Lime flavour 01620018 (contains: lime oil, maltodextrin, stabiliser E414).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

oPA/Al/PVC//Al blisters containing 7, 28, 49 or 56 sublingual tablets.
Or
oPA/Al/PVC//unit-dose blisters of 7x1, 28x1, 49x1 or 56x1 sublingual tablets.

Not all pack sizes may be marketed.

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

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/267/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authoristion: 20th December 2024

10 DATE OF REVISION OF THE TEXT

February 2025