SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buprenorphine/Naloxone Mylan 2 mg/0.5 mg sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 2 mg buprenorphine (as hydrochloride) and 0.5 mg naloxone (as hydrochloride dihydrate).

Excipient(s) with known effect:

Each sublingual tablet contains 39.90 mg lactose.

Each sublingual tablet contains 0,18 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet

White to off-white, round and biconvex tablets, with score line on one side and a diameter of about 6.5 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 indicated 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 must 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 must 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 two Buprenorphine/Naloxone Mylan 2 mg/0.5 mg. This may be achieved using two Buprenorphine/Naloxone Mylan 2 mg/0.5 mg as a single dose, which can be repeated up to twice 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 stabilisation and maintenance therapy
Following treatment induction on day 1, the patient must be rapidly stabilised on an adequate maintenance dose by titrating to achieve a dose that holds the patient in treatment and suppresses opioid withdrawal effects and is guided by reassessment of the clinical and psychological status of the patient. The maximum single daily dose should not exceed 24 mg buprenorphine.

During maintenance therapy, it may be necessary to periodically restabilise the patient on a new maintenance dose in response to changing patient needs.
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/2 mg may be given 16 mg/4 mg on alternate days, with no dose on the intervening days. In some patients, after a satisfactory stabilisation has been achieved, the frequency of dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose,

and the dose on Friday should be three times the individually titrated daily dose, with no dose on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg /day may not find this regimen adequate.

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

Switching between sublingual tablet and film (where applicable)
Patients being switched between buprenorphine/naloxone sublingual tablets and buprenorphine/naloxone film should be started on the same dose as the previously administered medicinal product. However, dose adjustments may be necessary when switching between medicinal products. Due to the potentially greater relative bioavailability of buprenorphine/naloxone film compared to buprenorphine/naloxone sublingual tablets, patients switching from sublingual tablets to film should be monitored for overdose. Those switching from film to sublingual tablets should be monitored for withdrawal or other indications of underdosing. In clinical studies, the pharmacokinetics of buprenorphine/naloxone film were not consistently shown to be similar to the respective dosage strengths of buprenorphine/naloxone sublingual tablets, as well as to the combinations (see section 5.2). If switching between buprenorphine/naloxone film and buprenorphine/naloxone sublingual tablets, the patient should be monitored in case a need to readjust the dose occurs. Combining different formulations or alternating between film and sublingual tablet formulations is not advised.

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 can be made up from multiple buprenorphine/naloxone 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.

Treatment goals and discontinuation
Before initiating treatment with Buprenorphine/Naloxone Mylan, 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/naloxone, 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 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

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/Naloxone Mylan. Abuse or intentional misuse of Buprenorphine/Naloxone Mylan 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/Naloxone Mylan 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.
Combining buprenorphine with naloxone in buprenorphine/naloxone is intended to deter misuse and abuse of the buprenorphine. Intravenous or intranasal misuse of buprenorphine/naloxone is expected to be less likely than with buprenorphine alone since the naloxone in this medicinal product 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 buprenorphine/naloxone 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/naloxone 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 medicinal 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.

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

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 effects of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a post-marketing study. Both buprenorphine and naloxone are extensively metabolised in the liver and plasma levels were found to be higher for both buprenorphine and naloxone in patients with moderate and severe hepatic impairment compared with healthy subjects. Patients should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity or overdose caused by increased levels of naloxone and/or buprenorphine.

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 greater risk of liver injury. Regular monitoring of liver function is recommended (see section 4.4).

Buprenorphine/naloxone 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.

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).

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).

Class effects
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, in other circumstances where cerebrospinal pressure may be increased, or in patients with a 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).

Serotonin syndrome
Concomitant administration of Buprenorphine/Naloxone Mylan 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.

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.

Buprenorphine/Naloxone Mylan 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’.

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

Paediatric population
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.

4.5 Interaction with other medicinal products and other forms of interaction

Buprenorphine/naloxone 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).

Buprenorphine/naloxone should be used cautiously when co-administered with:

O 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 medicinal product, and should also be cautioned to use benzodiazepines concurrently with this medicinal product only as directed by their physician (see section 4.4).

O 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 machines hazardous.

O 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.

O gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

O 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).

O CYP3A4 inhibitors: an interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC (area under the curve) of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving Buprenorphine/Naloxone Mylan 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).

O 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.

O The concomitant use of monoamine oxidase inhibitors (MAOI) might produce exaggeration of the effects of opioids, based on experience with morphine.

O 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.

O 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 or limited amount of data from the use of buprenorphine/naloxone 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.

Breast-feeding
It is unknown whether naloxone is excreted in human milk. Buprenorphine and its metabolites are excreted in human milk. In rats, buprenorphine has

been found to inhibit lactation. Therefore, breastfeeding should be discontinued during treatment with buprenorphine/naloxone .

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 adversely 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 studies 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			Anaemia	

lymphatic system disorders			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 Paraesthesia Somnolence	Amnesia Hyperkinesia Seizure Speech disorder Tremor	Hepatic encephalopathy Syncope
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	Dental caries
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 decreased	Blood creatinine increased	Transaminases increased
Injury, poisoning and procedural complications		Injury	Heat stroke	

Description of selected adverse reactions

In cases of intravenous drug misuse, some adverse reactions 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 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).

Drug dependence
Repeated use of Buprenorphine/Naloxone Mylan 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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Respiratory depression as a result of central nervous system depression is the primary symptom requiring intervention in the case of overdose because it may lead to respiratory arrest and death. 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 buprenorphine/naloxone produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Clinical efficacy and safety

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 versus 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 increasing 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. Buprenorphine Mean Pharmacokinetic Parameters.

Pharmacokinetic Parameter	buprenorphine/naloxone 4 mg	buprenorphine/naloxone 8 mg	buprenorphine/ naloxone 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)

Table 3. Changes in pharmacokinetic parameters for buprenorphine/naloxone film administered sublingually or buccally in comparison to buprenorphine/naloxone sublingual tablet

Dosage	PK Parameter	**Increase in Buprenorphine**			PK Parameter	**Increase in Naloxone**		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 × 2 mg/0.5 mg	C_{max}	22 %	25 %	-	C_{max}	-	-	-
	$AUC_{0\text{-last}}$	-	19 %	-	$AUC_{0\text{-last}}$	-	-	-
2 × 2 mg/0.5 mg	C_{max}	-	21 %	21 %	C_{max}	-	17 %	21 %
	$AUC_{0\text{-last}}$	-	23 %	16 %	$AUC_{0\text{-last}}$	-	22 %	24 %
1 × 8 mg/2 mg	C_{max}	28 %	34 %	-	C_{max}	41 %	54 %	-
	$AUC_{0\text{-last}}$	20 %	25 %	-	$AUC_{0\text{-last}}$	30 %	43 %	-
1 × 12 mg/3mg	C_{max}	37 %	47 %	-	C_{max}	57 %	72 %	9 %
	$AUC_{0\text{-last}}$	21 %	29 %	-	$AUC_{0\text{-last}}$	45 %	57 %	-
1 × 8 mg/2 mg plus	C_{max}	-	27 %	13 %	C_{max}	17 %	38 %	19 %
	$AUC_{0\text{-last}}$	-	23 %	-	$AUC_{0\text{-last}}$	-	30 %	19 %

2 × 2 mg/0.5 mg								

Note 1. '– 'represents no change when the 90 % confidence intervals for the geometric mean ratios of the C_{max} and $AUC_{0\text{-last}}$ values are within the 80 % to 125 % limit.
Note 2. There are no data for the 4 mg/1 mg strength film; it is compositionally proportional to the 2 mg/0.5 mg strength film and has the same size as the 2 × 2 mg/0.5 mg film strength.

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
Buprenorphine is primarily metabolised through 14-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
Elimination of buprenorphine is bi- or tri-exponential, and has a mean half-life from plasma of 32 hours.
Buprenorphine is excreted in the faeces (~70%) by biliary excretion of the glucuroconjugated metabolites the rest (~30%) being excreted in the urine.

Linearity/non-linearity
Buprenorphine C_{max} and AUC increased in a linear fashion with the increasing dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

<u>Naloxone</u>
Absorption and distribution
Following sublingual administration of buprenorphine/naloxone, plasma naloxone concentrations are low and decline rapidly. Naloxone mean peak plasma concentrations were too low to assess dose proportionality.
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.

Distribution
Naloxone is approximately 45 % protein bound, primarily to albumin.

Biotransformation

Naloxone 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.

Elimination
Naloxone is excreted in the urine, with a mean half-life of elimination from plasma ranging from 0.9 to 9 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 4 summarises the results from a clinical trial in which the exposure of buprenorphine and naloxone was determined after administering a buprenorphine/naloxone 2.0/0.5 mg sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 4. 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 agonist 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/m² 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/naloxone 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 mg/kg/day, 30 mg/kg/day and 120 mg/kg/day, with estimated exposure multiples of 3 times to 75 times, based on a human daily sublingual dose of 16 mg calculated on a mg/m² 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 (K = 29.7)

Citric acid monohydrate

Sodium citrate

Magnesium stearate

Acesulfame potassium

Lemon flavour (contains: flavouring preparations, maltodextrin, Acacia)

Lime flavour (contains: flavouring preparations, maltodextrin, Acacia).

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 or 28 sublingual tablets.
Unit-dose blisters of 7x1 or 28x1 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

Generics [UK] Limited t/a Mylan

Station Close

Potters Bar

Hertfordshire

EN6 1TL

United Kingdom

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