Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Subutex 8 mg sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains buprenorphine hydrochloride equivalent to buprenorphine base: 8 mg
Excipient(s) with known effect: Lactose monohydrate 191.76 mg/tablet

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sublingual tablet

8 mg: Uncoated oval white flat bevelled edged tablet, nominal dimensions 14 mm x 7 mm, B8 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology
Treatment with Subutex sublingual tablets is intended for use in adults and children over 15 years of age who have agreed to be treated for opioid dependence.

Treatment with Subutex sublingual tablets must be by physicians who have specialist training in its use and all treated patients must be on a central register according to Drug Misuse Programme guidelines. These physicians can be consultants, and/or Level I or Level II GPs who have received special training. All patients will be reviewed and reassessed regularly.

Precautions to be taken before dosing
Prior to treatment induction, physicians should be aware of the partial agonist profile of buprenorphine to the opiate receptors, which may precipitate a withdrawal syndrome in opioid-dependent patients and consideration should be given to the types of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with 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 patients dependent on heroin or short acting opioids**, the first dose of buprenorphine should be started when objective signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.

• **for patients receiving methadone:** before beginning Subutex therapy, the dose of methadone should be reduced to a maximum of 30mg/day. Subutex 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 0.8 to 4 mg, administered as a single daily dose.

Dosage adjustment and maintenance:
The dose of Subutex 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; this caution should be followed especially in patients being transferred from methadone to Subutex.

Dosage reduction and termination of treatment:
After a satisfactory period of stabilisation has been achieved, the dosage may be reduced gradually to a lower maintenance dose; when deemed appropriate, treatment may be discontinued in some patients. The availability of the sublingual tablet in doses of 0.4 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.

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 accelerated liver injury. Regular monitoring of liver function is recommended (see section 4.4).
Buprenorphine should be used with caution in patients with hepatic insufficiency (see section 5.2). In these patients titration of Subutex should be slower to allow for stabilisation.
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
No data are available in children under 15 years of age; therefore, Subutex should not be used in children under the age of 15.

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 the active substance(s) or to any of the excipients listed in section 6.1 Severe respiratory insufficiency
Severe hepatic insufficiency
Acute alcoholism or *delirium tremens*
Use during acute asthma attack
Head injury and increased intracranial pressure
Breast feeding

4.4 Special warnings and precautions for use

Subutex sublingual tablets are recommended only for the treatment of major opioid drug dependence. It is also recommended that treatment is prescribed by a physician who ensures comprehensive management of the opioid dependent patient(s).

It is important to follow recommendations for initiating treatment, dosage adjustment and monitoring of the patient (see section 4.2).

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 dug 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.

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.

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

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

Buprenorphine may cause severe, possibly fatal, respiratory depression in children who accidentally ingest it. Protect children against exposure.

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

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

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. Therefore, Subutex is a drug of addiction.

Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

Hepatitis, hepatic events
Cases of acute hepatic injury have been reported in opioid-dependent patients both in clinical trials and in postmarketing 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 Subutex and during treatment. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending on the findings, Subutex may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the drug treatment is continued, hepatic function should be monitored closely.

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

Hepatic impairment

The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a postmarketing study. Since buprenorphine is extensively metabolized, plasma levels were found to be elevated for buprenorphine in patients with moderate and severe hepatic impairment. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine. Subutex 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.

Serotonin syndrome
Concomitant administration of Subutex 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.

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).

Patients with lactose intolerance
This product contains lactose (see section 6.1). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Use in adolescents
Due to lack of data in adolescents (age 15 – 18), patients in this age group should be more closely monitored during treatment.
General warnings related to the administration of opioids
Opioids may cause orthostatic hypotension in ambulatory patients.

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

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

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

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

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

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

Subutex contains lactose and sodium.
Patients with rare hereditary problems of galactose intolerance, 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'.

4.5 Interaction with other medicinal products and other forms of interactions

Subutex should not be taken together with:

- alcoholic drinks or medications containing alcohol as alcohol increases the sedative effect of buprenorphine, which can make driving vehicles and operating machinery hazardous (see section 4.7).Subutex should be used cautiously together 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 risk of central nervous system depression is greatly increased when Subutex is abused by deliberate overdose, inhalation or intravenous administration. Patients who are taking Subutex should inform their physician before any elective anaesthesia procedures which may require the use of benzodiazepines or related drugs. Therefore, the concomitant prescription of benzodiazepines or related drugs with buprenorphine in the treatment of opiate dependence should be avoided unless medically necessary in the context of the comprehensive medical, social and psychological management strategy; the benefits outweigh the risks associated with concomitant use and patients are aware of the associated risks. The dose and duration of concomitant use should be limited (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 vehicles and operating 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. Patients with a need for analgesia and opioid dependence treatments may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists.
- 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.

- Serotonergic medicinal products:such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitor (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).
- Monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.

- CYP 3A4 inhibitors: An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased C_{max} and AUC of buprenorphine (approximately 50% and 70% respectively) and to a lesser extent, of the metabolite, norbuprenorphine. Patients receiving Subutex should be closely monitored and may require dose-reduction if combined with potent CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, or azole antifungals such as ketoconazole and itraconazole, or macrolide antibiotics).

- CYP3A4 inducers: Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in sub-optimal treatment of opioid dependence with buprenorphine. It is recommended that patients receiving Subutex should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin or rifampicin) are co-administered. The dose of either buprenorphine or the CYP3A4 inducer may need to be adjusted accordingly.

4.6 Fertility, pregnancy and lactation

Pregnancy
Buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.
Towards the end of pregnancy, buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Long-term administration during the last three months of pregnancy may cause a withdrawal syndrome in the neonate (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus or convulsions). The syndrome is generally delayed from several hours to several days after birth.
Due to the long half-life of buprenorphine, neonatal monitoring for several days should be considered at the end of pregnancy to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Breast-feeding
In animals buprenorphine passes into the mother's milk. Therefore, breast feeding should be discontinued during treatment with Subutex (see section 4.3).

4.7 Effects on ability to drive and use machines

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

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.

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

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Frequency not known**
Infections and infestations		Bronchitis Infection Influenza Pharyngitis Rhinitis	
Blood and lymphatic system disorders		Lymphadenopathy	
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders	Insomnia	Agitation Anxiety Depression Hostility	Drug dependence

		Nervousness Paranoia Thinking abnormal	
Nervous system disorders	Headache	Dizziness Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor	
Eye disorders		Lacrimal disorder Mydriasis	
Cardiac disorders		Palpitations	
Vascular disorders		Vasodilatation	
Respiratory, thoracic and mediastinal disorders		Cough Dyspnoea Yawning	
Gastrointestinal disorders	Nausea	Abdominal pain Constipation Diarrhoea Dry mouth Dyspepsia Gastrointestinal disorder Flatulence Tooth disorder Vomiting	
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash	
Musculoskeletal, connective tissue and bone disorders		Arthralgia Back pain Bone pain Muscle spasms Myalgia Neck pain	
Reproductive system and breast disorders		Dysmenorrhoea	
General disorders and administration site conditions	Drug withdrawal syndrome Pain	Asthenia Chest pain Chills Malaise Oedema peripheral Pyrexia	Drug withdrawal syndrome neonatal

Description of selected adverse reactions

The following is a summary of other post-marketing adverse event reports that are considered serious or otherwise noteworthy:

• In cases of intravenous misuse, local reactions, sometimes septic (abscess, cellulitis), and potentially serious acute hepatitis and other infections such as pneumonia, endocarditis have been reported (see section 4.4).

• In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

• The most common signs and symptoms of hypersensitivity include rashes, urticaria, and pruritus. Cases of bronchospasm, angioedema, and anaphylactic shock have been reported (see section 4.3).

• Transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy, and hepatic necrosis have occurred (see section 4.4).

• Neonatal drug withdrawal syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder than that seen with a full μ-opioid agonist and may be delayed in onset. The nature of the syndrome may vary depending upon the mother's drug use history (see section 4.6).

• Hallucination, orthostatic hypotension, urinary retention and vertigo have been reported.

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

Treatment
Naloxone may not be effective in reversing the respiratory depression produced by buprenorphine. Therefore, the primary management of overdose should be the re-establishment of adequate ventilation with the mechanical assistance of respiration, if required.

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 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. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

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.

Use of an opioid antagonist (i.e., naloxone at a dosage not exceeding 10 mg) 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. Doses of naloxone hydrochloride higher than 10mg may be of limited value and are not recommended in the management of buprenorphine overdose. Since most of overdose cases reported with buprenorphine were associated with concomitant abuse of other CNS depressants (e.g. benzodiazepines, certain anti-depressants, barbiturates, neuroleptics), measures appropriate for the overdose of any concomitant medications should be taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic group
Drugs used in opioid dependence ATC-code: N07BC01

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

Clinical efficacy and safety
Buprenorphine has a wide margin of safety due to its partial agonist/antagonist activity, which limits its depressant effects, particularly on cardiac and respiratory functions.

5.2 Pharmacokinetic properties

Absorption
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 doseconcentration 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.

5.3 Preclinical safety data

Chronic toxicity studied in four species (rodents and non rodents) by four different administration routes has not showed any clinically pertinent element. In one oral study of one year in dogs, a hepatic toxicity has been observed at very high dose (75 mg/kg).

Teratology studies conducted in rats and rabbits allow to conclude that buprenorphine is not embryotoxic nor teratogenic. No undesirable effect on fertility has been reported in rats, however a high peri- and post- natal mortality has been observed in this species by IM and oral administration routes, due to difficult parturition and impairment of maternal lactation.

In a standard series of tests, none proof of genotoxic potential has been evidenced.

Carcinogenicity studies in mice and rats show that there is no difference in the incidences of different tumour types between control and buprenorphine treated animals. However, in a study conducted with pharmacological doses in mice, an atrophy and a tubular mineralisation of testis have been evidenced in treated animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol (E421)
Maize Starch
Povidone K30
Citric acid
Sodium citrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 year.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.

6.5 Nature and contents of container

7 or 28 tablets in nylon/Aluminium/uPVC blister packs.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

6.6 Special precautions for disposal

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Indivior Europe Limited
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Dublin 2
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8 MARKETING AUTHORISATION NUMBER

PA22617/001/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Last date of authorisation: 28 April 2007

10 DATE OF REVISION OF THE TEXT

July 2021