SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Buprenorphine Bluefish 2 mg sublingual tablets.
Buprenorphine Bluefish 8 mg sublingual tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2 mg sublingual tablets:
Each sublingual tablet contains buprenorphine hydrochloride corresponding to 2 mg buprenorphine base.

8 mg sublingual tablets:
Each sublingual tablet contains buprenorphine hydrochloride corresponding to 8 mg buprenorphine base.

Excipient(s) with known effect:
2 mg sublingual tablets: Lactose 48 mg.

8 mg sublingual tablets: Lactose 191 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual Tablet

Appearance:
2 mg tablets: Oval, biconvex, white tablets with ”2” embossed on one side.
8 mg tablets: Oval, biconvex, white tablets with ”8” embossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Treatment must be under the supervision of a physician experienced in the management of opiate dependence/addiction.

Posology
Treatment with Buprenorphine Bluefish sublingual tablets is intended for use in adults and children over 15 years of age who have agreed to be treated for addiction to opioids.

Precautions to be taken prior to initiating treatment
When treatment with Buprenorphine Bluefish is initiated, the physician should be aware of the partial opioid receptor agonist profile of the buprenorphine molecule. Buprenorphine binds to μ and κ opioid receptors and may trigger withdrawal symptoms in opioid-dependent patients. Prior to starting

treatment, consideration should be given to the types of opioid dependence (i.e. long-or short-acting opioid), the time since last opioid use and the degree of opioid dependence. To avoid precipitating withdrawal, induction with Buprenorphine Bluefish should first be undertaken when objective and clear signs of withdrawal are evident.

- **for patients dependent on heroin or short acting opioids**, the first dose of buprenorphine should be started when objective signs of withdrawal appear, but not less than 6 hours after the patient last used opioids.
- **for patients receiving methadone:** before beginning Buprenorphine Bluefish therapy, the dose of methadone should be reduced to a maximum of 30 mg/day. Buprenorphine Bluefish 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 therapy
The initial dose is 0.8 to 4 mg administered as a single daily dose.

For doses not realisable/practicable with the 2 mg and 8 mg strengths, alternative buprenorphine medicinal products at lower strengths are available.

Dosage adjustment and maintenance
The dose of Buprenorphine Bluefish should be increased progressively according to the clinical effect of the individual patient. The dose should be titrated based on repeated assessment of clinical and psychological status; a dose of 8-16 mg daily is often sufficient. The maximum daily dose should not exceed 24 mg.

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. The availability of sublingual tablets in doses of 2 mg and 8 mg (and lower strengths available for other medicinal products), allows for a downward titration of the 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
Plasma levels of buprenorphine are increased in patients with moderate and severe hepatic impairment compared to healthy subjects (see section 5.2). Buprenorphine Bluefish should be used with caution in patients with moderate hepatic impairment and may require lower initial doses and careful dose titration. Patients should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine (see section 4.4). Buprenorphine Bluefish is contraindicated in patients with severe hepatic impairment (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, (creatinine clearance<30ml/min), which may require dose adjustment (see section 5.2).

Paediatric population
No data are available in children under 15 years of age; therefore, Buprenorphine Bluefish should not be used in children under the age of 15.

For further information, see the national guidelines for buprenorphine treatment.

Method of administration
Administration of Buprenorphine Bluefish is sublingual. The physician must advise the patient that the sublingual route is the only effective and safe route of administration for this medicinal product. The sublingual tablet is to be placed under the tongue until dissolved, which usually occurs within 5 to 10 minutes.
The tablet should not be swallowed, crushed or chewed.

Treatment goals and discontinuation
Before initiating treatment with Buprenorphine Bluefish, 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 Bluefish, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe respiratory insufficiency.
- Severe hepatic insufficiency.
- Acute alcoholism or delirium tremens.

4.4 Special warnings and precautions for use

Buprenorphine Bluefish sublingual tablets are recommended only for treatment of opioid drug dependence. National requirements should be followed with regard to dispensing. It is also recommended that treatment is prescribed by a physician who ensures comprehensive management of opioid dependent patients.

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 overdosing, 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 a new drug dependent individuals using buprenorphine as the primary drug of abuse, and may occur if the medicine is distributed for illicit use directly by the intended patient or if the medicine is not safeguarded against theft.
In cases of intravenous drug misuse, local reactions, sometimes septic (abscess, cellulitis) and potentially serious acute hepatitis and other acute infections, such as pneumonia and endocarditis have been reported.

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 and craving by self-medicating with opioids, alcohol or other sedative-hypnotics such as benzodiazepines.

To minimise the risk of misuse, abuse and diversion, physician 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 need.

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.
This product should be used with caution 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).
Patients with the physical and/or pharmacological risk factors above should be monitored, and dose reduction may be considered.
Buprenorphine 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 medicine in front of children. An emergency unit should be contacted immediately in case of accidental ingestion or suspicion of ingestion.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs
Concomitant use of buprenorphine and sedative medicines 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 buprenorphine concomitantly with sedative medicinal product, the lowest effective dose of the sedative medicines should be used and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Serotonin syndrome
Concomitant administration of Buprenorphine Bluefish 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 of the μ opiate receptor and long-term use cause opioid dependence. Studies in animals, as well as clinical experience, have shown that buprenorphine in chronic administration may produce dependence but to a lesser degree than full agonists (e.g. morphine). Abrupt discontinuation of treatment is not recommended as it may result in a withdrawal syndrome that may be delayed in onset.

Interactions
Combinations with CYP3A4 inhibitors such as erythromycin, ketoconazole, and ritonavir may result in strongly increased plasma concentrations of buprenorphine and this should therefore be avoided (see section 4.5).

Hepatitis and hepatic events
Cases of acute hepatic injury have been reported in opioid-dependent patients both in clinical trials and in post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of cytolytic hepatitis, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy and death. In many cases, the presence of pre-existing liver enzyme abnormalities, genetic disease, infection with hepatitis B or hepatitis C virus, alcohol abuse, anorexia, concomitant use of other potentially hepatotoxic drugs and ongoing injecting drug use may have had a causative or contributory role. These underlying factors must be taken into consideration before prescribing Buprenorphine Bluefish and during treatment. When a hepatic event is suspected, further clinical and etiological evaluation is required. Depending on the findings, Buprenorphine Bluefish 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 Bluefish, 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). Withdrawal symptoms may also be associated with sub-optimal dosing.

Allergic reactions
Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, urticaria, and pruritus. Cases of bronchospasm, angioedema, and anaphylactic shock have been reported in rare cases (see section 4.8). A history of hypersensitivity to buprenorphine is a contraindication to buprenorphine use.

Hepatic impairment
The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a single-dose post-marketing study. Since buprenorphine is extensively metabolized in the liver, 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. Buprenorphine Bluefish tablets should be used with caution in patients with moderate hepatic impairment and this may require lower initial dosing and careful titration. In patients with severe hepatic insufficiency the use of buprenorphine is contraindicated (See sections 4.3 and 5.2).

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

when dosing patients with severe renal impairment (creatinine clearance <30 ml/min) (see sections 4.2 and 5.2).

Use in adolescents
Due to the limited data in adolescents (age 15–18), patients in this age group should be especially closely monitored during treatment.

General opioid class warnings
Opioids can cause orthostatic hypotension.
Opioids may elevate cerebrospinal fluid pressure, which may cause seizures. As with other opioids, caution is needed in patients using buprenorphine and having head injury, intracranial lesions and increased cranial pressure, or history of seizure.
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 should be used with caution in patients with hypotension, prostatic hypertrophy or urethral stricture.
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.

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 Bluefish. Abuse or intentional misuse of Buprenorphine Bluefish 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 Bluefish 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.

Excipients
Buprenorphine Bluefish contains lactose (see section 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Buprenorphine Bluefish contains less than 1 mmol sodium (23 mg) per Buprenorphine 2mg and 8mg sublingual tablets, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Buprenorphine Bluefish should not be taken together with:

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

Buprenorphine Bluefish should be used cautiously together with:

- 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).

- 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 of sedative medicines should be limited (see section 4.4). Patients should be warned that it is extremely dangerous to self-medicate with benzodiazepines that have not specifically been prescribed by the treating physician for the purpose of concomitant use with Buprenorphine Bluefish.

- The concomitant use of Buprenorphine Bluefish with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

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

- 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 vehicles and operating machinery hazardous.

- 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.

- 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.

- *CYP3A4 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 norbuprenorphine.
  Patients receiving Buprenorphine Bluefish should be closely monitored and may require dose-reduction if combined with potent CYP3A4 inhibitors (such as protease inhibitors as ritonavir, nelfinavir and indinavir or azole antifungal agents such as ketoconazole, itraconazole, voriconazole or posaconazole; or macrolide antibiotics).

- *CYP3A4 inducers:*
  Concomitant use of CYP3A4 inducers with buprenorphine may decrease buprenorphine plasma concentrations, potentially resulting in sub-optimal treatment of opioid dependence with buprenorphine. Therefore, it is recommended that patients receiving Buprenorphine Bluefish should be closely monitored if enzyme inducers (such as phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered, and the dose of buprenorphine or CYP3A4 inducer may need to be adjusted accordingly.

- *Effect of buprenorphine on other medicinal products*

Buprenorphine has been shown to be a CYP2D6 and CYP3A4 inhibitor in vitro. The risk of inhibition with therapeutic concentrations seems low but can not be excluded. When buprenorphine (predominantly at high doses) is combined with medicinal products that are CYP2D6 or CY3A4 substrates the plasma levels of these medicinal products may rise and dose dependent undesirable effects may occur. Buprenorphine does not inhibit CYP2C19 in vitro. The effect on other enzymes that metabolises medicinal products has not been investigated.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate reproductive toxicity.

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

Towards the end of pregnancy, buprenorphine may induce respiratory depression in the new-born 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 a few days after birth. If the mother is treated up to the end of pregnancy, neonatal monitoring for several days after birth should be considered due to the long half-life of buprenorphine to prevent the risk of respiratory depression or withdrawal syndrome in neonates.

Breast-feeding
In rats, buprenorphine has been shown to inhibit lactation. Buprenorphine and its metabolites are excreted in human breast milk. Therefore breast-feeding should be discontinued during treatment with Buprenorphine Bluefish.

Fertility
There is no or limited data on the effects of buprenorphine on human fertility. Effects on animal fertility have been observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Buprenorphine Bluefish has moderate influence on the ability to drive and use machines when administered to opioid dependent patients.

Buprenorphine Bluefish can 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 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 trial were those related to withdrawal symptoms (e.g. insomnia, headache, nausea, and hyperhidrosis), as well as pain.

Tabulated list of adverse reactions
Table 1 summarizes adverse reactions reported with a higher incidence in patients treated with buprenorphine (n=103) during a pivotal clinical study versus placebo (n=107).

The frequency of possible side 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); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Table 1 also captures the most common adverse drug reactions reported by the MAH global safety database identified for all other clinical experience and post-marketing surveillance. The frequency of occurrence is unknown where an adverse drug reaction was not identified by the pivotal clinical trial.

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

System Organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Infection	Pharyngitis				
Immune system disorders						Hypersensitivity reactions[3]
Metabolism and nutrition disorders		Decreased appetite				
Psychiatric disorders	Insomnia	Agitation Anxiety Depression Hostility Nervousness Paranoia Thinking abnormal		Hallucination		Drug dependence
Nervous system disorders	Headache	Hyperkinesia Hypertonia Migraine Paraesthesia Somnolence Syncope Tremor Vertigo				
Eye disorders		Lacrimal disorder Mydriasis				
Cardiac disorders		Palpitations				
Vascular disorders		Vasodilatation Orthostatic hypotension				
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Respiratory depression[1]		Bronchial spasm
Gastrointestinal disorders	Nausea Abdominal pain	Constipation Vomiting Diarrhoea Dry mouth Dyspepsia Gastrointestinal disorder Flatulence				Dental caries

System Organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Hepatobiliary disorders				Necrosis of the liver		Transaminases increase Hepatitis, Jaundice[4]
Skin and subcutaneous tissue disorders	Hyperhidrosis	Rash				Angioedema
Musculoskeletal and connective tissue disorders		Back pain Musculoskeletal pain Muscle spasms				
Renal and urinary disorders				Urine retention		
Reproductive system and breast disorders		Dysmenorrhoea Leukorrhea				
General disorders and administration site conditions	Drug withdrawal syndrome	Asthenia				Drug withdrawal syndrome neonatal[2]

Description of selected adverse reactions

The following is a summary of post-marketing adverse event reports that are considered serious or otherwise noteworthy:
[1] Respiratory depression has occurred. Death due to respiratory depression has 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 CNS depressants such as alcohol or other opioids (See sections 4.4 and 4.5).
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.
[2] Neonatal withdrawal syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history (See section 4.6).
[3] The most common signs and symptoms of hypersensitivity include rashes, urticaria and pruritus. Cases of bronchospasm, respiratory depression, angioedema and anaphylactic shock have been reported.
[4] Transaminase increase, hepatitis, acute hepatitis, cytolytic hepatitis, jaundice, hepatorenal syndrome, hepatic encephalopathy, and hepatic necrosis have occurred (see section 4.4).

Drug dependence
Repeated use of [product name] 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 national reporting system listed in Appendix V.

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 (see section 4.4). Signs of overdose may also include sedation, miosis, hypotension, nausea, vomiting and/or disordered speech.

Treatment/Management
In the event of overdose, general supportive measures should be instituted, including close monitoring of the respiratory and cardiac status of the patient.
Symptomatic treatment of respiratory depression and standard intensive care measures, should be performed. A patent airway should be ensured and assisted or controlled ventilation should be implemented if necessary. 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 injectable opioid antagonist (i.e. naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine, buprenorphine being highly bound to the morphinic receptors.

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. Ongoing IV infusion rates should be titrated to patient response. If infusion is not possible, repeated dosing with naloxone may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Drugs used in opioid dependence, ATC code: N07 BC01

Mechanism of action
Buprenorphine is a partial opioid agonist/antagonist which attaches to the μ- and κ-receptors of the brain. Its activity in maintenance treatment of opioid dependence is attributed to its slowly reversible binding tothe μ-receptors which, over a longer period, might minimise the need of the addicted patients for drugs.

5.2 Pharmacokinetic properties

Absorption

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

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

Distribution

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

Biotransformation and elimination

Buprenorphine is primarily metabolised through N-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation. Norbuprenorphine is a μ-agonist with weak intrinsic activity.

The elimination of buprenorphine is bi- or tri- exponential, with a long terminal elimination phase of 20 to 25 hours, in part due to re-absorption 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.

Special populations

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone were evaluated in a single dose post-marketing study.
Table 2 summarizes the results from a clinical trial in which the exposure of buprenorphine was determined after administering a buprenorphine/naloxone 2.0/0.5mg sublingual tablet in healthy subjects, and in subjects with varied degrees of hepatic impairment.

Table 2. Effect of hepatic impairment on pharmacokinetic parameters of buprenorphine following buprenorphine/naloxone administration (change relative to health subjects)

PK Parameter	Mild Hepatic Impairment (Child-Pugh Class A) (n=9)	Moderate Hepatic Impairment (Child-Pugh Class B) (n=8)	Severe Hepatic Impairment (Child-Pugh Class C) (n=8)
Buprenorphine			
C_{max}	1.2-fold increase	1.1-fold Increase	1.7-fold increase
AUC_{last}	Similar to control	1.6-fold increase	2.8-fold increase

Overall, buprenorphine plasma exposure increased approximately 3-fold in patients with severely impaired hepatic function after the administration of a 2 mg single dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, reproduction toxicity, genotoxicity or carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Mannitol (E421)
Maize starch
Citric acid, anhydrous (E330)
Sodium citrate (E331)
Povidone (E1201)
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC/PVDC/Aluminium).

Pack sizes:
7, 14 and 28 sublingual tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION

<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

6 December 2024